



(86) Date de dépôt PCT/PCT Filing Date: 2006/10/02
(87) Date publication PCT/PCT Publication Date: 2007/09/13
(45) Date de délivrance/Issue Date: 2013/07/30
(85) Entrée phase nationale/National Entry: 2008/09/04
(86) N° demande PCT/PCT Application No.: JP 2006/319705
(87) N° publication PCT/PCT Publication No.: 2007/102241
(30) Priorités/Priorities: 2006/03/08 (JP2006-062078);
2006/08/08 (JP2006-215904)

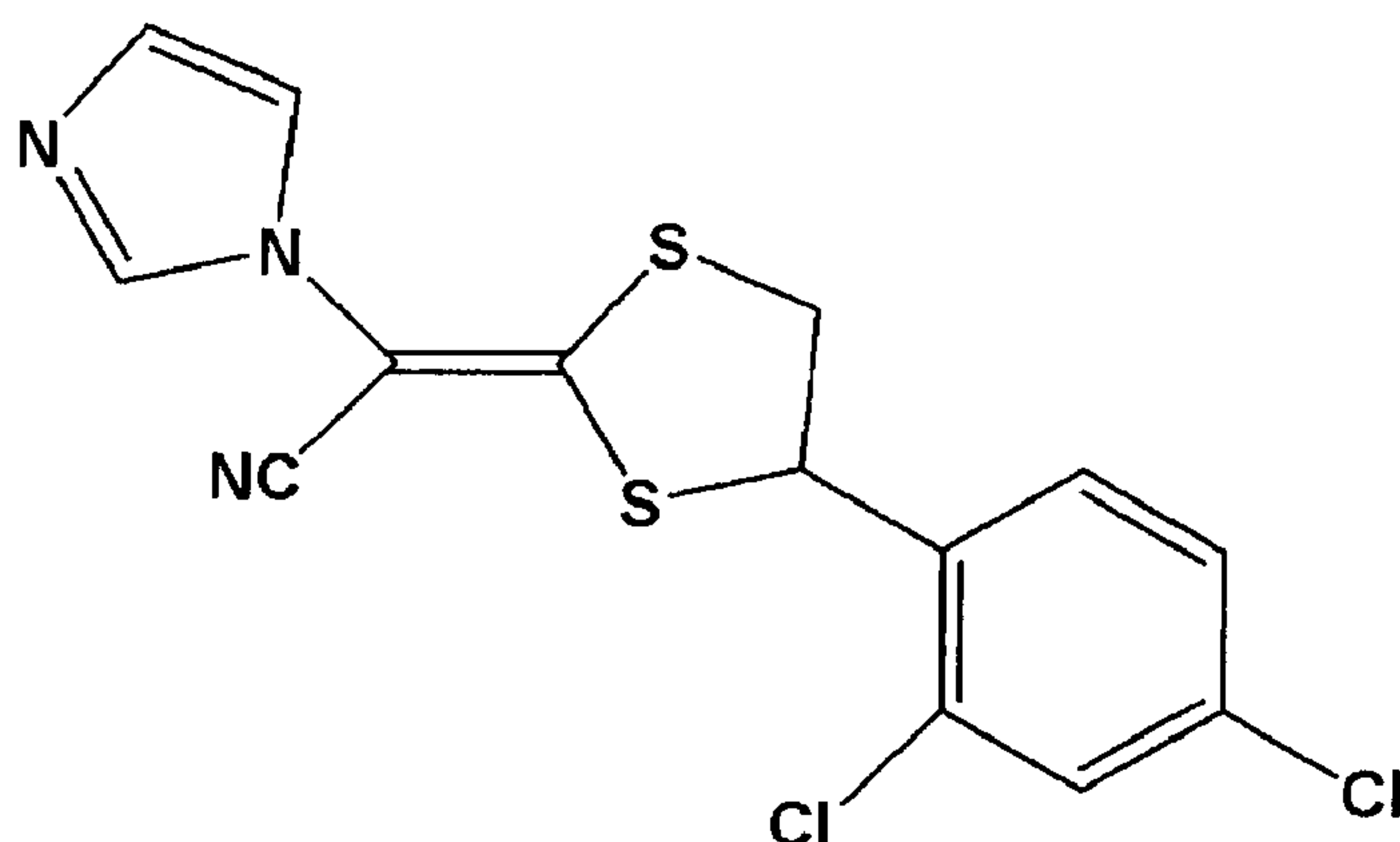
(51) Cl.Int./Int.Cl. *A61K 31/4178* (2006.01),
A61K 47/10 (2006.01), *A61K 47/12* (2006.01),
A61K 47/14 (2006.01), *A61K 47/22* (2006.01),
A61P 31/10 (2006.01)

(72) Inventeurs/Inventors:
MIKI, TOYOHICO, JP;
NOZAWA, AKIRA, JP;
KUBOTA, NOBUO, JP;
TOMIYAMA, SUSUMU, JP;
KOBAYASHI, HIROKAZU, JP

(73) Propriétaires/Owners:
NIHON NOHYAKU CO., LTD., JP;
POLA PHARMA INC., JP

(74) Agent: SMART & BIGGAR

(54) Titre : COMPOSITION PHARMACEUTIQUE POUR USAGE EXTERNE
(54) Title: PHARMACEUTICAL COMPOSITION FOR EXTERNAL USE



Structural formula (1)

(57) Abrégé/Abstract:

An external pharmaceutical composition characterized by containing 1) luliconazole of the following structural formula (1) and/or its salt and 2) an α -hydroxycarboxylic acid and/or its salt. Structural formula (1):

(12) 特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
国際事務局(43) 国際公開日
2007 年 9 月 13 日 (13.09.2007)

PCT

(10) 国際公開番号
WO 2007/102241 A1

(51) 国際特許分類:

A61K 31/4178 (2006.01) A61K 47/14 (2006.01)
A61K 47/10 (2006.01) A61K 47/22 (2006.01)
A61K 47/12 (2006.01) A61P 31/10 (2006.01)

(21) 国際出願番号: PCT/JP2006/319705

(22) 国際出願日: 2006 年 10 月 2 日 (02.10.2006)

(25) 国際出願の言語: 日本語

(26) 国際公開の言語: 日本語

(30) 優先権データ:

特願 2006-062078 2006 年 3 月 8 日 (08.03.2006) JP
特願 2006-215904 2006 年 8 月 8 日 (08.08.2006) JP

(71) 出願人 (米国を除く全ての指定国について): 日本農薬株式会社 (NIHON NOHYAKU CO., LTD.) [JP/JP]; 〒1038236 東京都中央区日本橋 1 丁目 2 番 5 号 Tokyo (JP). 株式会社ポーラファルマ (POLA PHARMA INC.) [JP/JP]; 〒1410031 東京都品川区西五反田 8-9-5 Tokyo (JP).

(72) 発明者; および

(75) 発明者/出願人 (米国についてのみ): 三木 豊彦 (MIKI, Toyohiko) [JP/JP]; 〒2440812 神奈川県横浜市戸塚区柏尾町 560 番地 ポーラ化成工業株式会社 戸塚研究所内 Kanagawa (JP). 野沢 暁 (NOZAWA, Akira) [JP/JP]; 〒2440812 神奈川県横浜市戸塚区柏尾町 560 番地 ポーラ化成工業株式会社 戸塚研究所内 Kanagawa (JP). 久保田 信雄 (KUBOTA, Nobuo) [JP/JP]; 〒2440812 神奈川県横浜市戸塚区柏尾町 560 番地 ポーラ化成工業株式会社 戸塚研究所内 Kanagawa (JP). 富

山 進 (TOMIYAMA, Susumu) [JP/JP]; 〒2440812 神奈川県横浜市戸塚区柏尾町 560 番地 ポーラ化成工業株式会社 戸塚研究所内 Kanagawa (JP). 小林 浩一 (KOBAYASHI, Hirokazu) [JP/JP]; 〒2440812 神奈川県横浜市戸塚区柏尾町 560 番地 ポーラ化成工業株式会社 戸塚研究所内 Kanagawa (JP).

(74) 代理人: 川口 嘉之, 外 (KAWAGUCHI, Yoshiyuki et al.); 〒1030004 東京都中央区東日本橋 3 丁目 4 番 10 号 アクロポリス 21 ビル 6 階 Tokyo (JP).

(81) 指定国 (表示のない限り、全ての種類の国内保護が可能): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

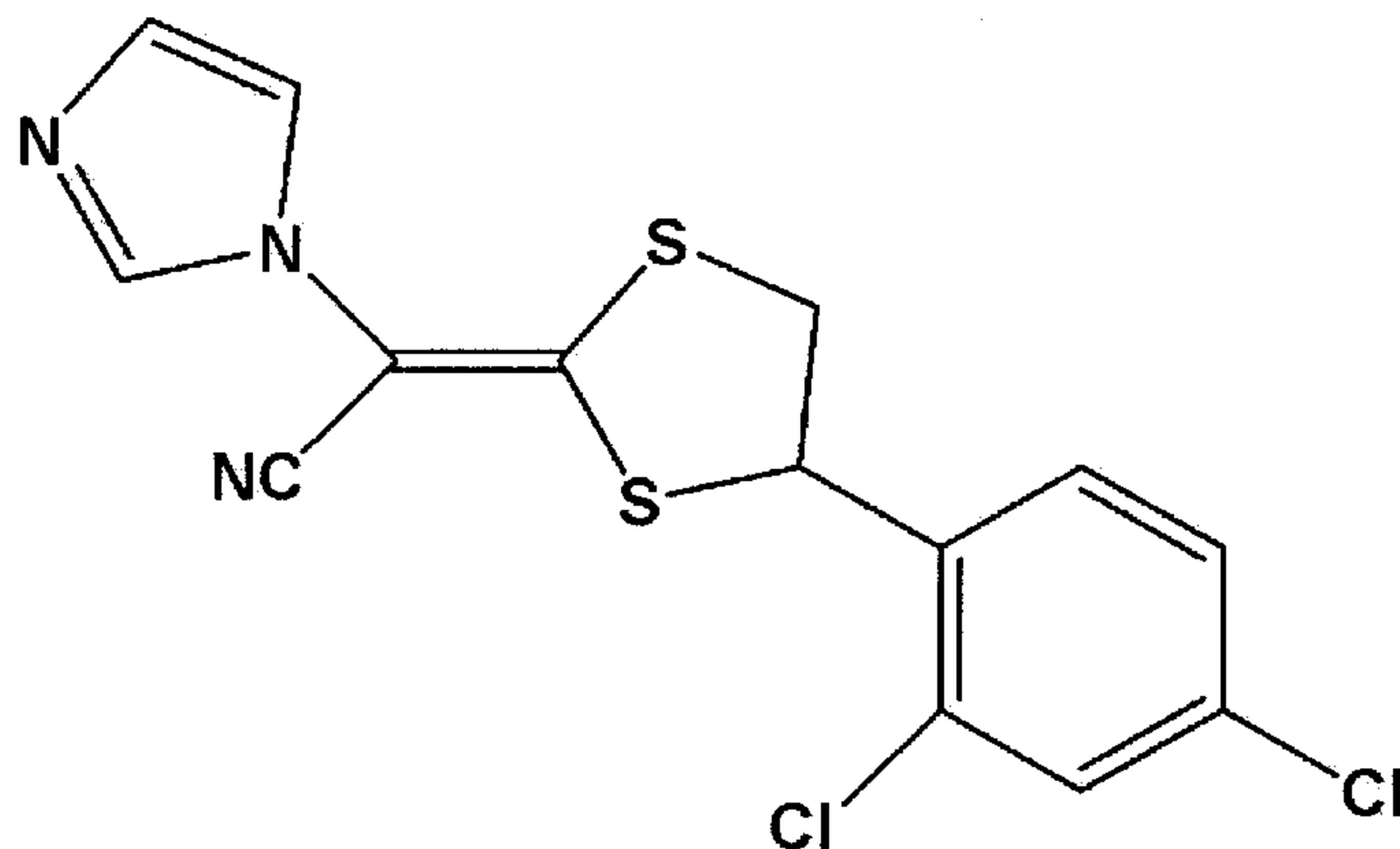
(84) 指定国 (表示のない限り、全ての種類の広域保護が可能): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), ユーラシア (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

添付公開書類:
— 国際調査報告書

[続葉有]

(54) Title: EXTERNAL PHARMACEUTICAL COMPOSITION

(54) 発明の名称: 外用の医薬組成物



(1)

(57) Abstract: An external pharmaceutical composition characterized by containing 1) luliconazole of the following structural formula (1) and/or its salt and 2) an α -hydroxycarboxylic acid and/or its salt. Structural formula (1):

[続葉有]

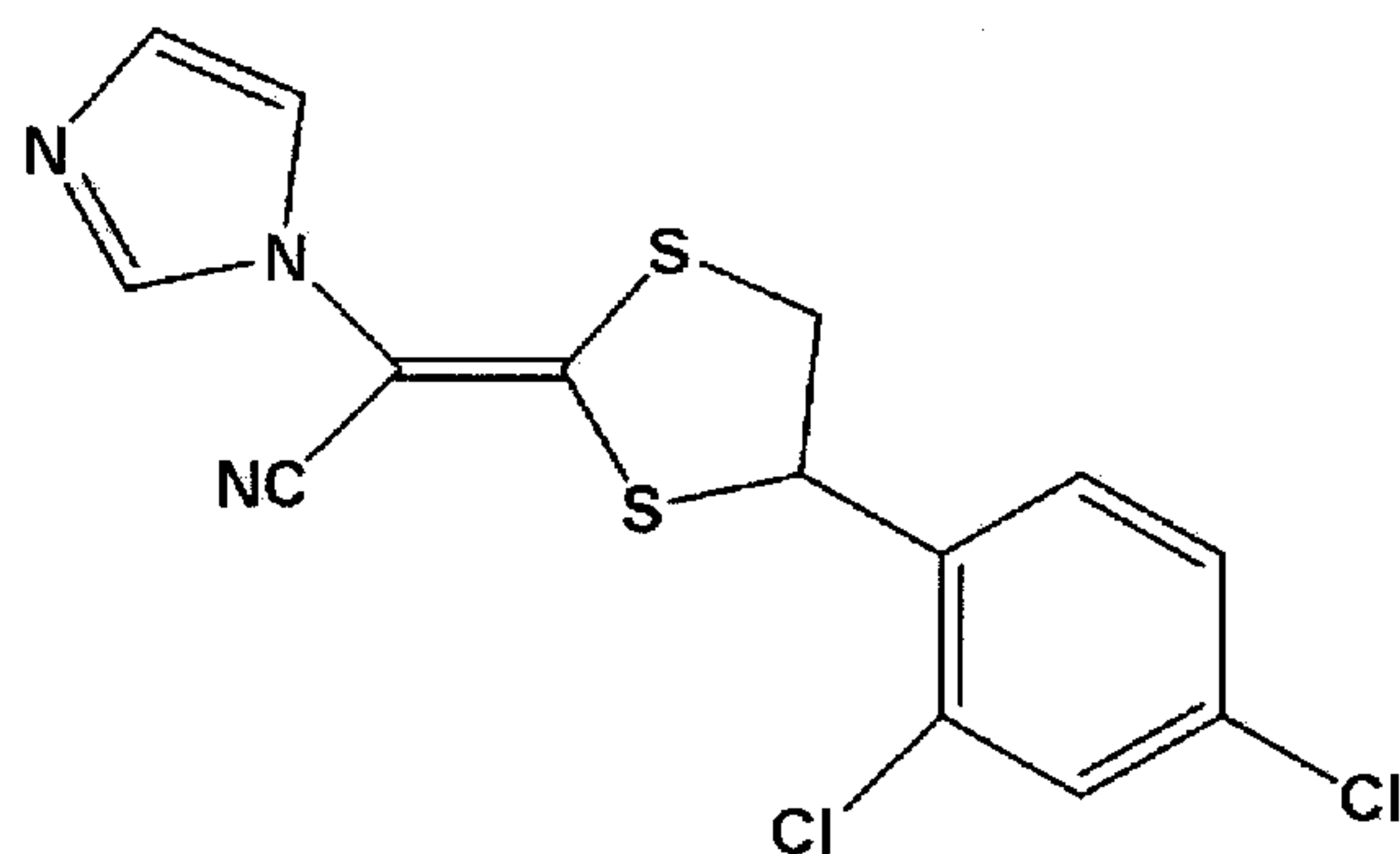
WO 2007/102241 A1



2文字コード及び他の略語については、定期発行される各*PCT*ガゼットの巻頭に掲載されている「コードと略語のガイダンスノート」を参照。

(57) 要約:

1) 下記構造式(1)で表されるルリコナゾール及び／またはその塩と、2) α -ヒドロキシカルボン酸及び／またはその塩とを含有することを特徴とする、外用の医薬組成物。



構造式 (1)

OP-C6061-PCT

DESCRIPTION

PHARMACEUTICAL COMPOSITION FOR EXTERNAL USE

Technical Field

[0001] The present invention relates to a pharmaceutical composition for external use, and more particularly, to a pharmaceutical composition for external use for treatment or prevention of onychomycosis or hyperkeratotic trichophytosis.

Background Art

[0002] The Japanese archipelago extends from a subtropical zone to a temperate zone and has a warm climate high in humidity, which is liable to facilitate propagation of fungi such as molds. In addition, due to westernization of clothes, people are now accustomed to wearing shoes on feet. Accordingly, a foot serves as a favorable environment for the propagation of the fungi, leading to mycotic skin diseases that are serious social issues nowadays. Of those, onychomycosis has a low complete cure rate and high relapsing and reinfection rates. Therefore, an effective therapy has been demanded.

Conventionally, treatments mainly using tolnaftate formulations have been conducted on such diseases. In recent years, imidazole-based antifungal agents, such as bifonazole and itraconazole, are mainly used.

As the imidazole-based antifungal agents, there are

OP-C6061-PCT

commercially available imidazole-based antifungal agents such as those represented by the general formula (1) described below, specifically, luliconazole represented by the structural formula (1) below and laniconazole represented by the structural formula (2) below. The above-mentioned luliconazole is currently the newest imidazole-based antifungal agent, and a commercially available product called "Lulicon" (registered trademark) is also present (e.g., see Patent Document 1 and Patent Document 2).

The luliconazole is an imidazole-based antifungal agent having optical activity, and has a wide antifungal spectrum, in particular, remarkable antifungal activity against dermatophytes. In addition, the luliconazole is also characterized by having extremely high retention property in the stratum corneum, and is a composition thus expected for application to the treatment of onychomycosis. However, nail acts as barrier to penetration of external materials including chemical substances, antifungal agents hardly reaches a region where the pathogenic fungi are present. Therefore, the above-mentioned luliconazole alone is insufficient to exert effects on the onychomycosis.

[0003] On the other hand, as means for accelerating percutaneous absorption of a material having antifungal activity, such as the above-mentioned luliconazole, benzyl alcohol has been known to be used as a penetration accelerator.

Further, in the field of antifungal agents, in addition to

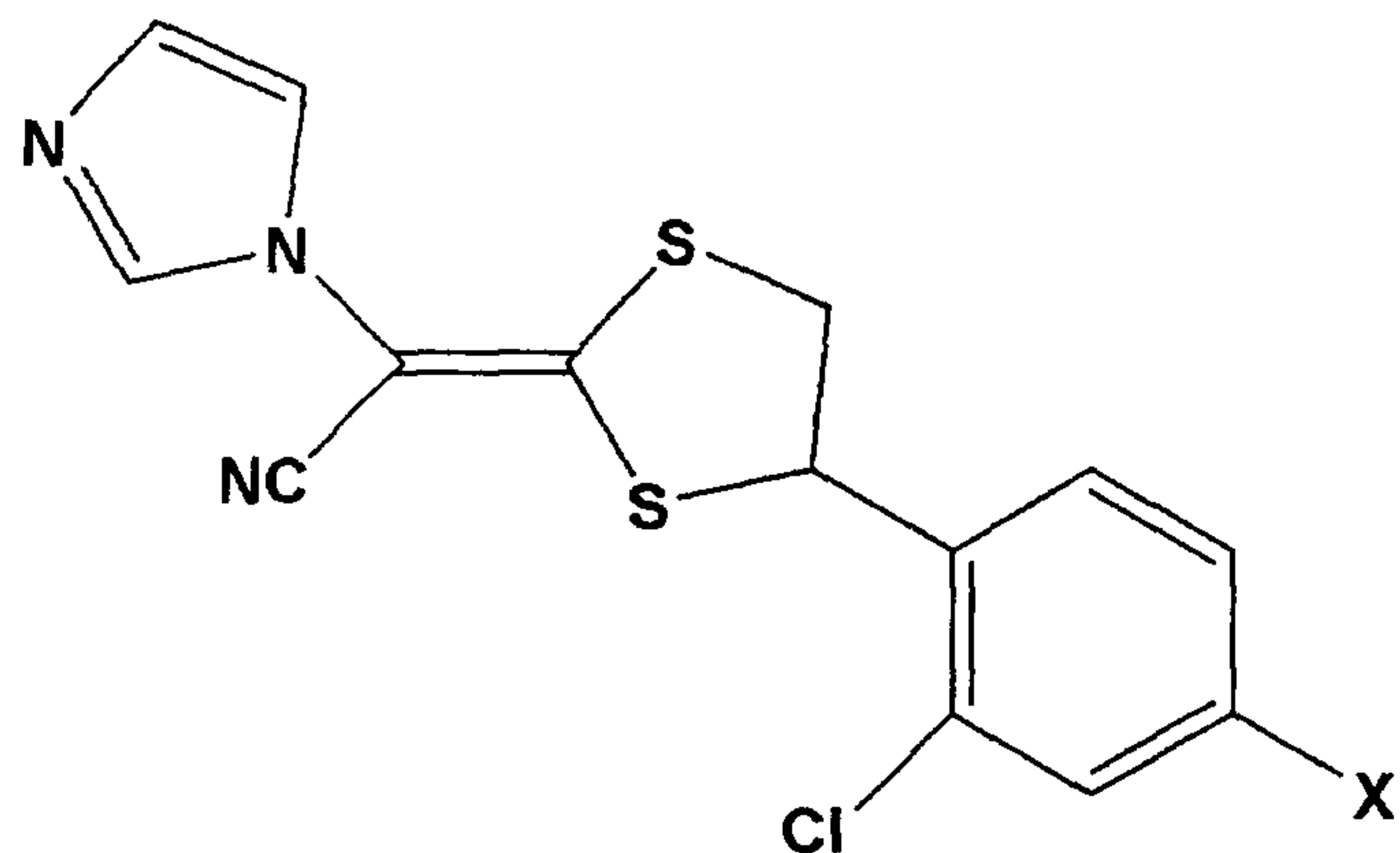
OP-C6061-PCT

the above-mentioned benzyl alcohol, means for facilitating the agent to proceed into the nail have been known in the art, including: a method of combining materials for softening the nail, such as urea and salicylic acid (e.g., see Patent Document 3 and Patent Document 4); a method using fatty acid ester (e.g., see Patent Document 5 and Patent Document 6); and a method of utilizing absorption-promoting agents, such as higher alcohol, organic base, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO). However, in any of the cases, the effects were not sufficient.

[0004] Further, as an attempt to treat onychomycosis by means of a compound represented by the general formula 1 below, a method of forming a reservoir layer by combining a film-forming agent with a polyoxypropylene/polyoxyethylene copolymer (e.g., see Patent Document 9) has been developed, resulting in significant improvement in effect thereof. However, when the nail becomes hard after recovering from the onychomycosis to some extent, there is a disadvantage in that a decrease in effect occurs.

[0005] [Chem 1]

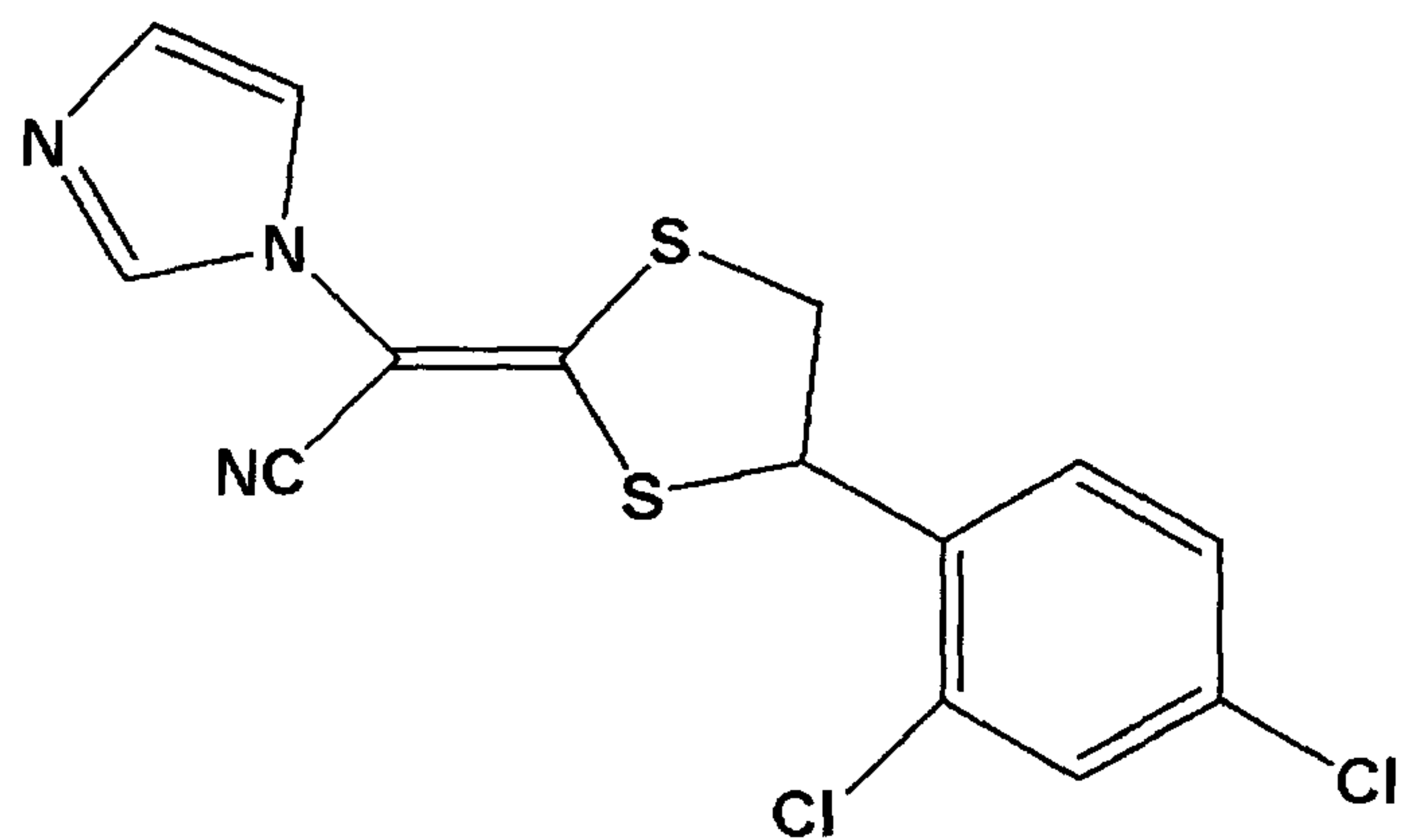
OP-C6061-PCT



General formula (1)

(where X represents a hydrogen atom or a chloride atom)

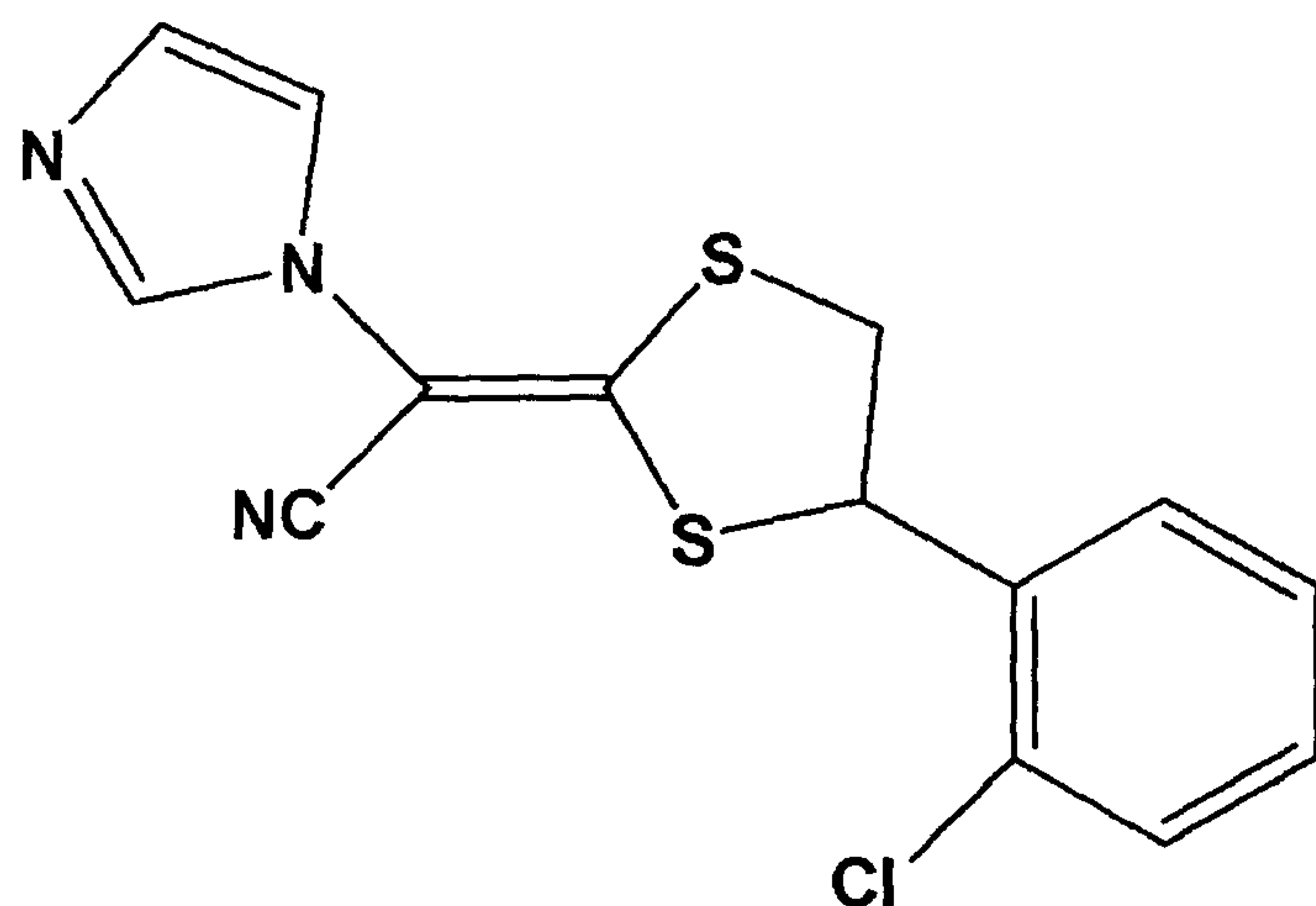
[0006] [Chem 2]



Structural formula (1)

[0007] [Chem 3]

OP-C6061-PCT



Structural formula (2)

[0008] Patent Document 1: JP 62-93227 A

Patent Document 2: JP 10-226686 A

Patent Document 3: JP 10-152433 A

Patent Document 4: JP 10-226639 A

Patent Document 5: JP 07-206711 A

Patent Document 6: WO 96/11710

Patent Document 7: JP 06-211651 A

Patent Document 8: JP 2004-529923 A

Patent Document 9: WO 03/105841

Disclosure of the Invention

Problem to be solved by the Invention

[0009] As described above, it is known that a material having antifungal activity, such as luliconazole, has difficulty in percutaneous absorption, and that benzyl alcohol or the like is used as a penetration accelerator as means for accelerating the percutaneous absorption. However, the present inventors have found

OP-C6061-PCT

that in the above-mentioned luliconazole, the benzyl alcohol or the like does not exert a sufficient effect of accelerating the penetration.

The present invention has been made based on the above-mentioned finding, and therefore has an object to provide a pharmaceutical composition for external use having excellent penetration and absorption properties by finding out a factor that inhibits the penetration and absorption properties of the pharmaceutical composition for external use containing luliconazole and/or a salt thereof, and developing means for eliminating the inhibitory factor.

Means for solving the Problems

[0010] In consideration of the above-mentioned circumstances, as a result of intensive studies for finding out a factor that inhibits the penetration-absorption of luliconazole and/or a salt thereof into a living body, the present inventors have found that a fine crystal of luliconazole is instantaneously precipitated when a pharmaceutical preparation containing as effective components luliconazole and/or a salt thereof is applied onto the living body, and that the precipitation of the crystal inhibits the penetration-absorption. Further, as a result of further intensive studies, the present inventors have found that the precipitation of the crystal can be suppressed by an addition of α -hydroxycarboxylic acid and/or a salt thereof, such as lactic acid, thereby completing

OP-C6061-PCT

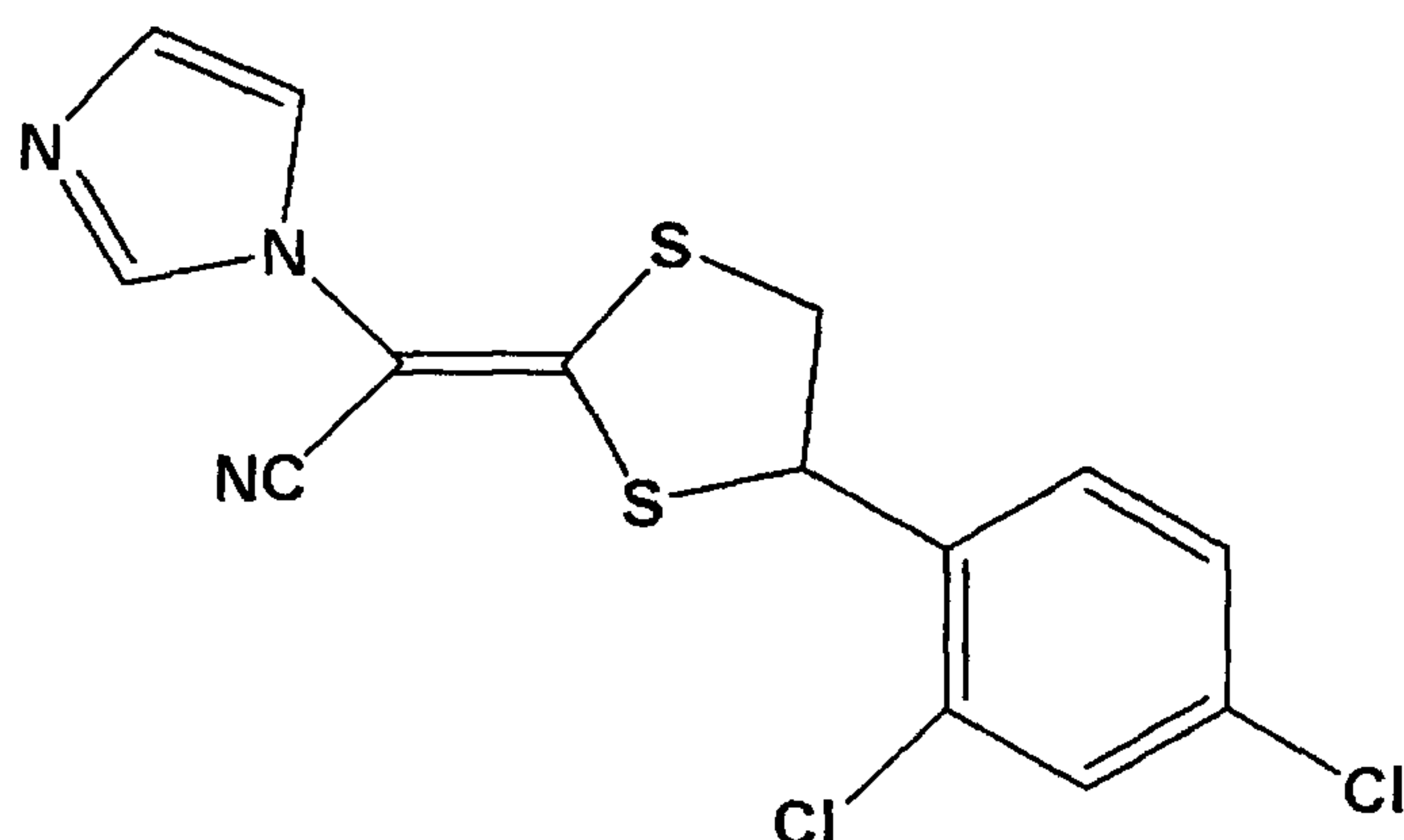
the present invention. In other words, the present invention is as follows.

(1) A pharmaceutical composition for external use, including:

(i) luliconazole represented by the following structural formula (1) and/or a salt thereof; and

(ii) α -hydroxycarboxylic acid and/or a salt thereof.

[0011] [Chem 4]



Structural formula (1)

[0012] (2) A pharmaceutical composition for external use according to the above-mentioned item (1), in which the α -hydroxycarboxylic acid is lactic acid, glycolic acid, or malic acid.

(3) A pharmaceutical composition for external use according to the above-mentioned item (1) or (2), in which the α -hydroxycarboxylic acid is lactic acid.

(4) A pharmaceutical composition for external use according to the above-mentioned item (1), further including benzyl alcohol.

72689-179

(5) A pharmaceutical composition for external use according to the above-mentioned item (1), further including diester of dibasic acid.

5 (6) A pharmaceutical composition for external use according to the above-mentioned item (5), in which the diester of dibasic acid is a diester of dibasic acid and alcohol having 1 to 4 carbon atoms.

10 (7) A pharmaceutical composition for external use according to the above-mentioned item (5), in which the diester of dibasic acid is a diethyl ester or diisopropyl ester of adipic acid or sebacic acid.

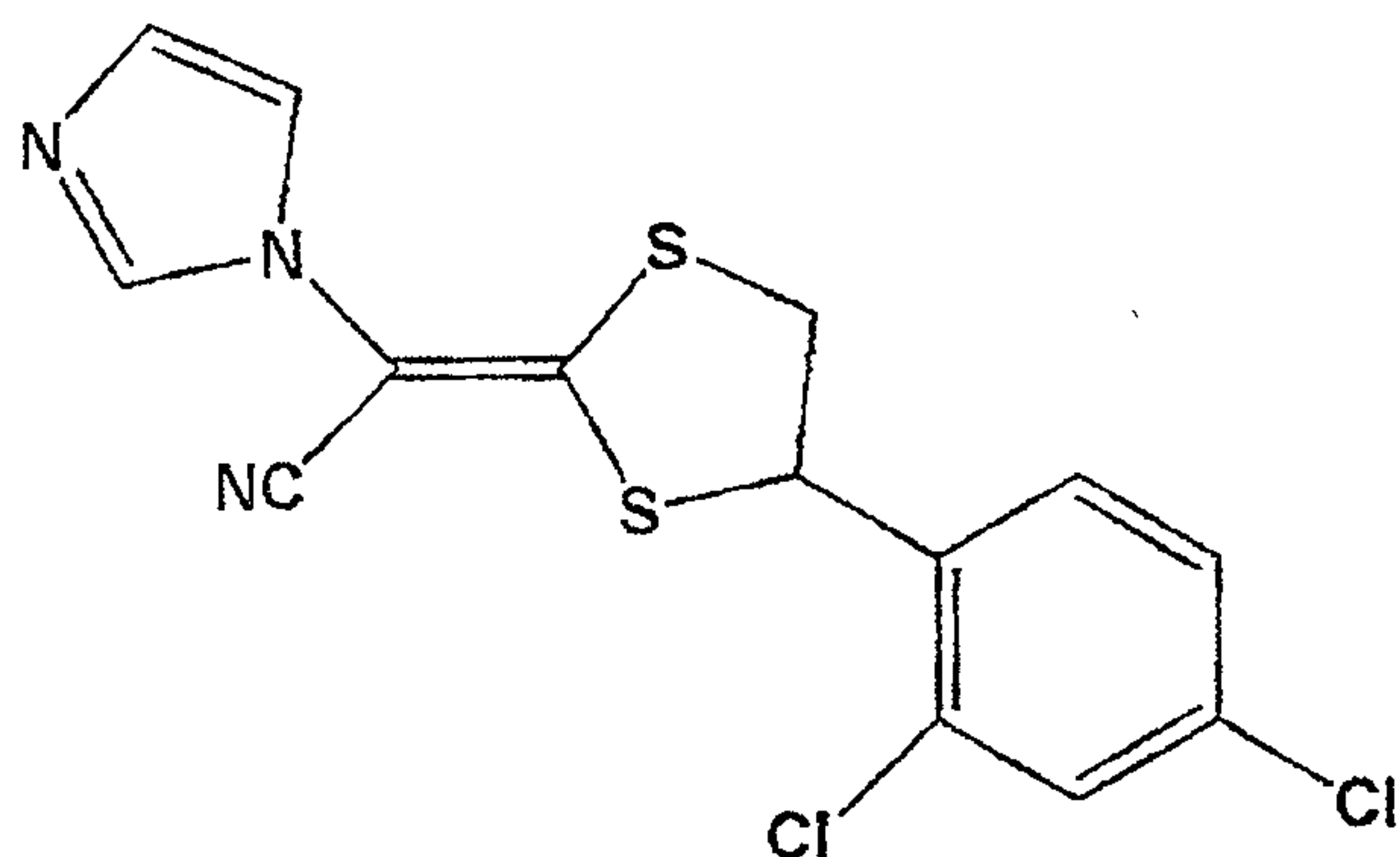
(8) A pharmaceutical composition for external use according to the above-mentioned item (1), further including N-methyl-2-pyrrolidone.

15 (9) A pharmaceutical composition for external use according to the above-mentioned item (1) to, which is provided for treatment or prevention of onychomycosis.

20 (10) A pharmaceutical composition for external use according to above-mentioned item (1), which is provided for treatment or prevention of horny-outgrowing type hyperkeratotic trichophytosis.

(11) A pharmaceutical composition for external use, comprising: (i) luliconazole represented by the following structural formula (1) and/or a salt thereof; wherein the
25 composition comprises luliconazole in an amount of 0.5 to 15 % by mass;

72689-179



Structural formula (1)

(ii) 1 to 10 % by mass lactic acid and/or salt thereof; and
(iii) ethanol, wherein the concentration of ethanol is
50 to 90 % by mass.

- 5 [0013] According to the present invention, it is possible to develop means for suppressing a factor that inhibits the acceleration of the penetration-absorption in an external preparation containing

OP-C6061-PCT

a compound represented by the general formula 1 and/or a salt thereof so as to provide an antifungal pharmaceutical composition excellent in penetration-absorption.

Brief Description of the Drawings

[0014] Fig. 1 is a microphotographic view of Lotion 4 of Example 4.

Fig. 2 is a microphotographic view of comparative Lotion 4 of Example 4.

Fig. 3 is a microphotographic view of comparative Lotion 5 of Example 4.

Fig. 4 is a microphotographic view of Lotion 5 of Example 5.

Fig. 5 is a microphotographic view of comparative Lotion 6 of Example 5.

Fig. 6 is a microphotographic view of comparative Lotion 7 of Example 5.

Best Mode for carrying out the Invention

[0015] (1) Luliconazole and/or a salt thereof as essential components of a pharmaceutical composition for external use (hereinafter, referred to as pharmaceutical composition of the present invention)

The pharmaceutical composition for external use according to the present invention contains as essential components luliconazole and/or a salt thereof (hereinafter, also referred to as luliconazole or the like). The above-mentioned luliconazole is represented by

OP-C6061-PCT

the above-mentioned structural formula (1). The above-mentioned luliconazole is a known compound represented by (R)-(-)-(E)-[4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene]-1-imidazolyl acetonitrile. Its manufacturing method and the antifungal properties are already known in the art. JP 62-93227 A (Patent Document 1 above) can be used as reference.

In addition, "salt thereof" is not specifically limited as far as it is physiologically acceptable. Preferable examples thereof include: mineral acid salts such as hydrochloride, nitrate, sulfate, and phosphate; organic acid salts such as citrate, oxalate, lactate, and acetate; and sulfuric acid-containing salts such as mesilate and tosilate. In terms of safety and solubility, hydrochloride is more preferable.

In the pharmaceutical composition for external use according to the present invention, the content of luliconazole or the like is preferably 0.1 to 30% by mass, more preferably 0.5 to 15% by mass in total with respect to the total amount of the pharmaceutical composition. The content of luliconazole or the like can be determined based on its solubility and formulation characteristics.

[0016] (2) α -hydroxycarboxylic acid and/or a salt thereof used in pharmaceutical composition for external use according to the present invention

The pharmaceutical composition for external use according to the present invention contains α -hydroxycarboxylic acid and/or a

OP-C6061-PCT

salt thereof (hereinafter, also referred to as α -hydroxycarboxylic acid or the like) as an essential component. The α -hydroxycarboxylic acid may be, for example, any of α -hydroxycarboxylic acids having 2 to 5 carbon atoms. Of those, lactic acid, glycolic acid, and malic acid can be preferably exemplified. In particular, of those, lactic acid is preferable. Further, those salts are not specifically limited as far as they can be used for pharmaceutical preparations and are physiologically acceptable. Preferable examples thereof include: alkali metal salts, such as sodium salt and potassium salt; alkaline earth metal salts, such as calcium salt and magnesium salt; organic amine salts, such as ammonium salt, triethylamine salt, and triethanolamine salt; and basic amino acid salts, such as arginine salt and lysine salt. The pharmaceutical composition for external use according to the present invention can contain only one kind of those components or two or more in combination.

In the pharmaceutical composition for external use according to the present invention, when applied, the component acts to suppress crystallization and precipitation of luliconazole or the like on the applied surface. Such an insoluble matter such as crystal or precipitation suppressing action allows luliconazole or the like to be absorbed into the body without any interruption. Therefore, the penetration-promoting agent, such as the benzyl alcohol, can fully exert its function.

Such an action cannot be sufficiently attained with acids other

OP-C6061-PCT

than α -hydroxycarboxylic acids. For exerting such an action, the content of α -hydroxycarboxylic acid in the pharmaceutical composition for external use according to the present invention is 0.1 to 20% by mass, preferably 1 to 10% by mass in total with respect to the total amount of the pharmaceutical composition. This is because the above-mentioned action may not be exerted if it is too low, and the effect reaches the limit and may restrict the mixing amounts of other components if it is too high.

Further, for exerting the insoluble matter such as crystal or precipitation suppressing action of luliconazole or the like by the α -hydroxycarboxylic acid or the like, the mass ratio of α -hydroxycarboxylic acid or the like to luliconazole or the like (i.e., α -hydroxycarboxylic acid or the like / luliconazole or the like) is preferably 0.1 to 10, more preferably 0.5 to 5, particularly preferably 0.8 to 2.

[0017] (3) Benzyl alcohol used in pharmaceutical composition for external use according to the present invention

The pharmaceutical composition for external use according to the present invention preferably contains benzyl alcohol. The benzyl alcohol is already used as an additive in pharmaceutical compositions and is commercially available, so it can be obtained with ease. In the presence of the α -hydroxycarboxylic acid or the like, the benzyl alcohol exerts actions of suppressing precipitation of crystals of luliconazole or the like on a living body upon

OP-C6061-PCT

application to also suppress inhibition of the penetration thereof into the living tissue, particularly into the nail. Therefore, the combination of benzyl alcohol with α -hydroxycarboxylic acid synergistically improves the orientation of agents to the nail matrix. For exerting such an action, the content of benzyl alcohol is preferably 0.5 to 15% by mass, particularly preferably 1 to 10% by mass with respect to the total amount of the pharmaceutical composition. In other words, if the content of benzyl alcohol is outside the above-mentioned range, luliconazole or the like may be crystallized and precipitated at the time of application. Therefore, as the crystallization and precipitation are suppressed at the time of application, the benzyl alcohol fully exerts its original effect of accelerating tissue penetration.

[0018] (4) Diester of dibasic acid used in pharmaceutical composition for external use according to the present invention

The pharmaceutical composition for external use according to the present invention preferably contains a diester of dibasic acid, in particular, any of diesters of dibasic acids and alcohols having 1 to 4 carbon atoms. Examples of the dibasic acids include those having 1 to 10 carbon atoms, preferably, adipic acid, sebacic acid, oxalic acid, and carbonic acid. On the other hand, preferable examples of the alcohols having 1 to 4 carbon atoms include methyl alcohol, ethyl alcohol, propyl alcohol, isopropyl alcohol, butyl alcohol, isobutyl alcohol, and tert-butyl alcohol. Alternatively,

OP-C6061-PCT

any of polyalcohols, such as ethylene glycol and propylene glycol may be used as the alcohol having 1 to 4 carbon atoms.

Specifically, preferable examples of diesters of the above-mentioned dibasic acids include propylene carbonate, diethyl adipate, diisopropyl adipate, diethyl sebacate, and diisopropyl sebacate. Of those, diisopropyl adipate and diethyl sebacate are particularly preferable. The pharmaceutical composition for external use according to the present invention can contain a single kind of those components or two or more in combination. In the presence of the α -hydroxycarboxylic acid or the like, the component, together with the benzyl alcohol and N-methyl-2-pyrrolidone described later, exerts its actions of promoting penetration of luliconazole or the like into the living tissue, particularly into the nail. For exerting such an action, in the pharmaceutical composition for external use according to the present invention, the content of the component is preferably 1 to 30% by mass, more preferably 5 to 15% by mass in total with respect to the total amount of the pharmaceutical composition.

[0019] (5) N-methyl-2-pyrrolidone used in pharmaceutical composition for external use according to the present invention

The pharmaceutical composition for external use according to the present invention preferably contains N-methyl-2-pyrrolidone.

The N-methyl-2-pyrrolidone is already used as an additive in pharmaceutical compositions and is commercially available, so it

OP-C6061-PCT

can be obtained with ease. In the presence of the α -hydroxycarboxylic acid or the like, N-methyl-2-pyrrolidone, together with the benzyl alcohol, diester of dibasic acid, or the like, exerts its actions of promoting penetration of luliconazole or the like into the living tissue, particularly into the nail. For exerting such an action, in the pharmaceutical composition for external use according to the present invention, the content of the component is preferably 1 to 15% by mass, particularly preferably 3 to 10% by mass with respect to the total amount of the pharmaceutical composition. N-methyl-2-pyrrolidone also has a function of preventing luliconazole from being transformed into an isomeric form during storage.

[0020] (6) Pharmaceutical composition for external use according to the present invention

In the pharmaceutical composition for external use according to the present invention, benzyl alcohol, diester of dibasic acid, and N-methyl-2-pyrrolidone exert their respective synergetic effects on the pharmaceutical composition for external use containing luliconazole or the like and α -hydroxylic acid or the like, so any one of those may be used in combination. However, they have their own mechanisms to accelerate the penetration of the pharmaceutical composition for external use containing luliconazole or the like and α -hydroxylic acid or the like into the nail, so it is preferable that those compounds be used in a form of containing

OP-C6061-PCT

at least benzyl alcohol, more preferably a combination of two or more in the form of containing at least benzyl alcohol, particularly preferably in the form of containing benzyl alcohol, diester of dibasic acid, and N-methyl-2-pyrrolidone. This is because the benzyl alcohol provides the pharmaceutical composition for external use containing luliconazole or the like and α -hydroxylic acid or the like with a significant synergetic effect (penetration-accelerating effect). Further, N-methyl-2-pyrrolidone also has a function of preventing luliconazole or the like from being transformed into an isomeric form during storage as well as a penetration-accelerating effect, and the stability of the above-mentioned pharmaceutical composition over time can be thus improved.

[0021] The pharmaceutical composition for external use according to the present invention can contain any of components commonly used in pharmaceutical compositions in addition to those described above, as far as it does not impair the effects according to the present invention.

Preferable examples of such components include: hydrocarbons such as vaseline and microcrystalline wax; esters such as jojoba oil, cetaceum, triacetin, triethyl citrate, and butyl acetate; triglycerides such as beef tallow and olive oil; higher alcohols such as cetanol and oleyl alcohol; fatty acids such as stearic acid and oleic acid; alcohols such as ethanol and isopropanol;

OP-C6061-PCT

polyalcohols such as glycerin and 1,3-butanediol; water; non-ionic surfactants; anionic surfactants; cationic surfactants; amphoteric surfactants; thickeners such as polyvinyl pyrrolidone and carbopol; preservatives; UV absorbers; antioxidants; pigments; and powders. Those optional components and the above-mentioned component are treated by common procedures, whereby a pharmaceutical composition for external use according to the present invention can be produced. The pharmaceutical composition for external use according to the present invention is not specifically limited as far as it is formulated into any of forms used for pharmaceutical compositions for external use, and preferable examples thereof include lotions, emulsions, gelatinizing agents, cream pharmaceuticals, aerosols, nail enamel agents, and hide gel patches. Of those, the lotions are most preferable. For stabilizing the clarity and color of solution such as luliconazole, 50 to 90% by mass of ethanol is most preferably contained.

[0022] The pharmaceutical composition for external use according to the present invention is preferably used for treating mycotic diseases or preventing progression of the diseases by using characteristics of luliconazole or the like. The mycotic diseases include: foot trichophytosis such as athlete's foot; trichophytosis corporis such as candida and pityriasis versicolor; and trichophytosis on a hard keratin portion, such as onychomycosis. Because of remarkable effects, it is particularly preferable to

OP-C6061-PCT

use the pharmaceutical composition for external use according to the present invention for treating the hard keratin portion, such as onychomycosis. In particular, the pharmaceutical composition for external use according to the present invention exerts preferable effects on the nail and such an effect is also exerted on typical dermatomycosis. Therefore, the application of a pharmaceutical composition for external use against dermatomycosis, which satisfies the configuration according to the present invention, is also within the technical scope according to the present invention. Examples of such dermatomycosis include trichophytosis such as foot trichophytosis, particularly horny-outgrowing type hyperkeratotic trichophytosis which appears on heels or the like. The present invention has a significant effect on the horny-outgrowing type hyperkeratotic trichophytosis, on which the conventional agents hardly exert their effects, among the above-mentioned dermatomycosis, which is preferable.

With regard to its use, for example, the pharmaceutical composition is applied on a diseased portion one or several times a day and the treatment is preferably carried out day after day. In particular, for onychomycosis, luliconazole or the like, which is an effective component in an amount that cannot be attained by normal formulation, can be transferred into the nail. Therefore, onychomycosis can be treated only by the external application without having to drink an antifungal agent over a long period of time.

OP-C6061-PCT

In addition, recurrence and reinfection have been a major problem for onychomycosis. However, the recurrence and reinfection can be prevented by administration of the pharmaceutical composition for external use according to the present invention for 1 to 2 weeks after abatement of the symptom. Therefore, the pharmaceutical composition for external use according to the present invention exerts preventive efficacy in this aspect.

Examples

[0023] Hereinafter, the present invention will be described in more detail with reference to examples. However, the present invention is not limited to those examples.

[0024] (Examples 1 to 3 and Comparative Examples 1 to 3)

Lotions 1 to 3 containing the pharmaceutical compositions according to the present invention and Comparative Lotions 1 to 3 were prepared on the basis of the formulations shown in Table 1 below. That is, formulation components were dissolved by mixing at room temperature while stirring, thereby preparing each lotion. After the application of each lotion, the formulation-stabilizing action thereof was investigated. In other words, one drop of each of Lotions 1 to 3 and Comparative Lotions 1 to 3 was dropped on a slide glass and then air-dried for five minutes, followed by microscopic observation to determine the degree of insoluble matter such as crystal or precipitation.

[0025] [Table 1]

OP-C6061-PCT

Components	% by mass					
	Lotion 1	Lotion 2	Lotion 3	Comparative Lotion 1	Comparative Lotion 2	Comparative Lotion 3
Luliconazole	1	3	5	1	3	5
Lactic acid	1	4	8	-	-	-
Ethanol	98	93	87	99	97	95
Total	100	100	100	100	100	100
insoluble matter such as crystal or precipitation	N/A	N/A	N/A	Detected	Detected	Detected

[0026] (Example 4 and Comparative Examples 4 and 5)

Lotion 4 containing the pharmaceutical compositions according to the present invention was prepared on the basis of the formulation shown in Table 2 below. That is, formulation components were dissolved by mixing at room temperature while stirring, thereby preparing Lotion 4.

[0027] [Table 2]

Components	% by mass
Luliconazole	5
Benzyl alcohol	2
Lactic acid	4
Ethanol	89
Total	100

[0028] In the formulation of Example 4, Comparative Lotion 4 (Comparative Example 4) in which lactic acid was replaced with ethanol and Comparative Lotion 5 (Comparative Example 5) in which lactic acid was replaced with phosphoric acid were prepared, respectively. Subsequently, those lotions as well as Lotion 4 were investigated for their formulation-stabilizing actions after application. In other words, one drop of each of Lotion 4, Comparative Lotion 4,

OP-C6061-PCT

and Comparative Lotion 5 was dropped on a slide glass and then air-dried for five minutes, followed by microscopic observation to determine the degree of insoluble matter such as crystal or precipitation. The degree of insoluble matter such as crystal or precipitation was calculated as an area ratio of a precipitated crystal to the area of one microscopic view field (means of three view fields). The results were 0% in Lotion 4, 11% in Comparative Lotion 4, and 9% in Comparative Lotion 5, respectively. Figs. 1 to 3 show microscopic photographs of Lotion 4, Comparative Lotion 4, and Comparative Lotion 5, respectively. Accordingly, it is found that Lotion 4, which contains the pharmaceutical composition according to the present invention, is suppressed in its insoluble matter such as crystal or precipitation on the applied surface.

Further, for Lotion 4 and Comparative Lotion 4 described above, the amount of agent that has penetrated through the nail was measured. In other words, front and back sides of a piece of a human nail were sandwiched by polytetrafluoroethylene plates provided with O-shaped rings (2 mm in inner diameter), and the plates were then fixed on Franz cells (open-top cells, Central Riken K.K.), respectively. Agar was injected into the cell on the backside of the nail and then fixed, followed by applying 0.5 μ L of the sample in the O-shaped ring on the cell on the front side of the nail. The application was performed once a day for three days. After 24 hours from the last application, the nail in the O-shaped ring was

OP-C6061-PCT

punched out and luliconazole was then extracted with methanol. The extract was determined for the amount of luliconazole in the nail by a high-performance liquid chromatographic method. Consequently, the amount of agent that has penetrated through the nail with respect to Comparative Lotion 4 was 0.60 when the amount of agent that has penetrated through the nail with respect to Lotion 4 was 1 (the amount of agent that has penetrated through the nail with respect to Lotion 4 was 1.67 when the amount of agent that has penetrated through the nail with respect to Comparative Lotion 4 was 1).

[0029] (Example 5 and Comparative Examples 6 and 7)

According to Table 3 below, Lotion 5 was prepared in a manner similar to that of Example 4. In the formulation of Example 5, Comparative Lotion 6 (Comparative Example 6) in which lactic acid was replaced with ethanol and Comparative Lotion 7 (Comparative Example 7) in which lactic acid was replaced with phosphoric acid were prepared, respectively. Subsequently, each of those lotions as well as Lotion 5 were subjected to a calculation of a ratio of crystalline areas in a manner similar to that of Example 4. The results were 0% in Lotion 5, 4% in Comparative Lotion 6, and 7% in Comparative Lotion 7, respectively. Figs. 4 to 6 show microscopic photographs of Lotion 5, Comparative Lotion 6, and Comparative Lotion 7, respectively. Here, the effects of the present invention were also recognized.

[0030] [Table 3]

OP-C6061-PCT

Components	% by mass
Luliconazole	5
Diisopropyl adipate	12
Lactic acid	4
Ethanol	79
Total	100

[0031] (Examples 6 and 7 and Comparative Example 8)

According to Table 4 below, Lotion 6 (Example 6) was prepared in a manner similar to that of Example 4. In the formulation of Example 6, Lotion 7 (Example 7) in which benzyl alcohol of Lotion 6 was replaced with ethanol and Comparative Lotion 8 (Comparative Example 8) in which benzyl alcohol and lactic acid of Lotion 6 were replaced with ethanol were prepared, respectively. They were subjected to measurement of the amount of agent that has permeated through the nail in a manner similar to that of Example 4. Consequently, the amount of agent that has penetrated through the nail with respect to Lotion 6 was 6.30 when that of Lotion 7 was 1 (the amount of agent that has penetrated through the nail with respect to Lotion 6 was 58 μg per 1 cm^3 of the nail, while that of Lotion 7 was 9.2 μg), while the amount of agent that has penetrated through the nail with respect to Comparative Lotion 8 was 0.61. In other words, it is found that the addition of lactic acid alone and the addition of both lactic acid and benzyl alcohol lead to 1.65- and 10.40-fold increase in penetrability of luliconazole into the nail. In consideration of those results together with those of Example 4 described above, it is found that in the pharmaceutical

OP-C6061-PCT

composition of the present invention, a penetration-accelerating agent such as benzyl alcohol exerts an original penetration-accelerating effect. Therefore, it is also found that the pharmaceutical composition of the present invention preferably contains such a component. Hereinafter, as an indicator for penetration-absorption, the amount of agent that has penetrated through the nail with respect to each sample when that of the control samples such as Lotion 7 is 1 is referred to as "penetration-absorbance ratio".

[0032] [Table 4]

Components	% by mass
Luliconazole	1
Benzyl alcohol	4
Ethanol	93.5
Lactic acid	1
Polyvinyl pyrrolidone	0.5
Total	100

[0033] (Examples 8 to 13)

According to Table 5 below, Lotions 8 to 13 containing the pharmaceutical composition of the present invention were prepared in a manner similar to that of Example 4. They were subjected to measurement of the amount of agent that has penetrated through the nail in a manner similar to that of Example 4. Consequently, the amount of agent that has penetrated through the nail (penetration-absorbance ratio) with respect to each of Lotions 8 to 13 when the amount of agent that has penetrated through the nail

OP-C6061-PCT

with respect to Lotion 7 was 1 was determined. The results are shown in Table 6. It is found that the pharmaceutical composition of the present invention preferably contains diester of dibasic acid, such as diisopropyl adipate. Any of those is known as a component for accelerating percutaneous absorption in dermal external preparations or the like. As for the penetration of luliconazole through the nail, in particular, it is found that diester of dibasic acid showed significant efficacy.

[0034] [Table 5]

Components	% by mass
Luliconazole	1
Component shown in Table 6	10
Ethanol	87.5
Lactic acid	1
Polyvinyl pyrrolidone	0.5
Total	100

[0035] [Table 6]

Sample	Component	Penetration-absorbance ratio
Lotion 8	Diisopropyl adipate	9.57
Lotion 9	Trans-cinnamic acid	1.53
Lotion 10	Propylene glycol	1.26
Lotion 11	Eugenol	1.11
Lotion 12	Trimethylphenol	1.70
Lotion 13	Octyldodecanol	2.14

[0036] (Examples 14 and 15)

According to Table 7 below, Lotion 14 containing the pharmaceutical composition of the present invention was prepared in a manner similar to that of Example 4. Simultaneously, Lotion

OP-C6061-PCT

15, in which benzyl alcohol of Lotion 14 was replaced with ethanol, was also prepared. Subsequently, the measurement of the amount of agent that has penetrated through the nail was carried out by the method described in Example 4 to obtain the amount of agent that has penetrated through the nail (penetration-absorbance ratio) with respect to each of Lotions 14 to 15 when the amount of agent that has penetrated through the nail with respect to Lotion 7 was 1. The penetration-absorbance ratio of Lotion 14 was 14.88 and the penetration-absorbance ratio of Lotion 15 was 4.19. From the result, it is found that in the pharmaceutical composition of the present invention, luliconazole is increased in penetrability through the nail by propylene carbonate. In addition, it is also found that the addition of benzyl alcohol leads to a 3.55-fold increase in penetrability.

[0037] [Table 7]

Components	% by mass
Luliconazole	1
Propylene carbonate	10
Ethanol	83.5
Benzyl alcohol	4
Lactic acid	1
Polyvinyl pyrrolidone	0.5
Total	100

[0038] (Examples 16 and 17)

According to Table 8 below, Lotion 16 containing the pharmaceutical composition of the present invention was prepared

OP-C6061-PCT

in a manner similar to that of Example 4. Simultaneously, Lotion 17, in which N-methyl-4-pyrrolidone of Lotion 16 was replaced with ethanol, was also prepared. Subsequently, the measurement of the amount of agent that has penetrated through the nail was carried out by the method described in Example 4 to obtain the amount of agent that has penetrated through the nail (penetration-absorbance ratio) with respect to Lotion 16 when the amount of agent that has penetrated through the nail with respect to Lotion 17 was 1. The penetration-absorbance ratio of Lotion 16 was 4.12, and further acceleration of agent penetrability as compared with that of Lotion 17 in which the penetrability of agent through the nail is accelerated by a combination of benzyl alcohol, diisopropyl adipate, and lactic acid was obtained. Therefore, an excellent effect of the addition of N-methyl-2-pyrrolidone was recognized. In other words, it is found that a particularly preferable mode of the pharmaceutical composition of the present invention contains lactic acid, diester of dibasic acid, benzyl alcohol, and N-methyl-2-pyrrolidone.

[0039] [Table 8]

Components	% by mass
Luliconazole	5
N-methyl-2-pyrrolidone	8
Ethanol	66.5
Lactic acid	4
Benzyl alcohol	4
Diisopropyl adipate	12
Polyvinyl pyrrolidone	0.5
Total	100

OP-C6061-PCT

[0040] (Example 18)

According to Table 9 below, Lotion 18 containing the pharmaceutical composition of the present invention was prepared in a manner similar to that of Example 4. The measurement of the amount of agent that has penetrated through the nail was carried out by the method described in Example 4 to obtain the amount of agent that has penetrated through the nail (penetration-absorbance ratio) with respect to Lotion 18 when the amount of agent that has penetrated through the nail with respect to Lotion 7 was 1, resulting in a penetration-absorbance ratio of 3.03. It is found that the pharmaceutical composition of the present invention has an excellent penetration-accelerating action. Even in the absence of benzyl alcohol, a combination of N-methyl-2-pyrrolidone and diisopropyl adipate allows an increase in permeability through the nail.

[0041] [Table 9]

Components	% by mass
Luliconazole	1
N-methyl-2-pyrrolidone	8
Diisopropyl adipate	10
Ethanol	76.5
Lactic acid	4
Polyvinyl pyrrolidone	0.5
Total	100

[0042] (Example 19)

According to Table 10 below, Lotion 19 containing the pharmaceutical composition of the present invention was prepared

OP-C6061-PCT

in a manner similar to that of Example 4. The measurement of the amount of agent that has penetrated through the nail was carried out by the method described in Example 4 to obtain the amount of agent that has penetrated through the nail (penetration-absorbance ratio) with respect to Lotion 19 when the amount of agent that has penetrated through the nail with respect to Lotion 7 was 1, resulting in a penetration-absorbance ratio of 2.49. It is found that the pharmaceutical composition of the present invention has an excellent penetration-accelerating action. Even in the absence of N-methyl-2-pyrrolidone, a combination of benzyl alcohol and diisopropyl adipate allows an increase in penetrability through the nail.

[0043] [Table 10]

Components	% by mass
Luliconazole	1
Benzyl alcohol	5
Diisopropyl adipate	10
Ethanol	79.5
Lactic acid	4
Polyvinyl pyrrolidone	0.5
Total	100

[0044] (Example 20)

According to Table 11 below, Lotion 20 containing the pharmaceutical composition of the present invention was prepared in a manner similar to that of Example 4. The measurement of the amount of agent that has penetrated through the nail was carried

OP-C6061-PCT

out by the method described in Example 4 to obtain the amount of agent that has penetrated through the nail (penetration-absorbance ratio) with respect to Lotion 20 when the amount of agent that has penetrated through the nail with respect to Lotion 7 was 1, resulting in a penetration-absorbance ratio of 2.49. It is found that the pharmaceutical composition of the present invention has an excellent penetration-accelerating action. This result indicates that diisopropyl adipate can be replaced with diethyl sebacate and the result of diisopropyl adipate can be applied to generally all of dibasic acid diesters.

[0045] [Table 11]

Components	% by mass
Luliconazole	1
Benzyl alcohol	5
Diethyl sebacate	10
Ethanol	79.5
Lactic acid	4
Polyvinyl pyrrolidone	0.5
Total	100

[0046] (Example 21)

According to Table 12 below, Lotion 21 containing the pharmaceutical composition of the present invention was prepared in a manner similar to that of Example 4. The measurement of the amount of agent that has penetrated through the nail was carried out by the method described in Example 4 to obtain the amount of agent that has penetrated through the nail (penetration-absorbance

OP-C6061-PCT

ratio) with respect to Lotion 21 when the amount of agent that has penetrated through the nail with respect to Lotion 7 was 1, resulting in a penetration-absorbance ratio of 2.34. It is found that the pharmaceutical composition of the present invention has an excellent penetration-accelerating action. In the pharmaceutical composition of the present invention, it can be seen that the penetration-accelerating effect by the solvent appears clearly.

[0047] [Table 12]

Components	% by mass
Luliconazole	1
Benzyl alcohol	5
Triacetin	10
Ethanol	79.5
Lactic acid	4
Polyvinyl pyrrolidone	0.5
Total	100

[0048] (Example 22)

According to Table 13 below, Lotion 22 containing the pharmaceutical composition of the present invention was prepared in a manner similar to that of Example 4. The measurement of the amount of agent that has penetrated through the nail was carried out by the method described in Example 4 to obtain the amount of agent that has penetrated through the nail (penetration-absorbance ratio) with respect to Lotion 22 when the amount of agent that has penetrated through the nail with respect to Lotion 7 was 1, resulting in a penetration-absorbance ratio of 2.05. It is found that the

OP-C6061-PCT

pharmaceutical composition of the present invention has an excellent penetration-accelerating action. In the pharmaceutical composition of the present invention, it can be seen that the penetration-accelerating effect by the solvent appears clearly.

[0049] [Table 13]

Components	% by mass
Luliconazole	1
Benzyl alcohol	5
Triethyl citrate	10
Ethanol	79.5
Lactic acid	4
Polyvinyl pyrrolidone	0.5
Total	100

[0050] (Example 23)

According to Table 14 below, Lotion 23 containing the pharmaceutical composition of the present invention was prepared in a manner similar to that of Example 4. The measurement of the amount of agent that has penetrated through the nail was carried out by the method described in Example 4 to obtain the amount of agent that has penetrated through the nail (penetration-absorbance ratio) with respect to Lotion 23 when the amount of agent that has penetrated through the nail with respect to Lotion 7 was 1, resulting in a penetration-absorbance ratio of 1.68. It is found that the pharmaceutical composition of the present invention has an excellent penetration-accelerating action. In the pharmaceutical composition of the present invention, it can be seen that the

OP-C6061-PCT

penetration-accelerating effect by the solvent appears clearly.

[0051] [Table 14]

Components	% by mass
Luliconazole	1
Benzyl alcohol	5
Butyl acetate	10
Ethanol	79.5
Lactic acid	4
Polyvinyl pyrrolidone	0.5
Total	100

[0052] (Example 24)

According to Table 15 below, Lotion 24 containing the pharmaceutical composition of the present invention was prepared in a manner similar to that of Example 4. The measurement of the amount of agent that has penetrated through the nail was carried out by the method described in Example 4 to obtain the amount of agent that has penetrated through the nail with respect to Lotion 24, resulting in 260.3 $\mu\text{g}/\text{cm}^3$. It is found that the pharmaceutical composition of the present invention has an excellent penetration-accelerating action.

[0053] [Table 15]

Components	% by mass
Luliconazole	1
N-methyl-2-pyrrolidone	8
Benzyl alcohol	4
Diisopropyl adipate	10
Ethanol	72.5
Lactic acid	4
Polyvinyl pyrrolidone	0.5
Total	100

OP-C6061-PCT

Industrial Applicability

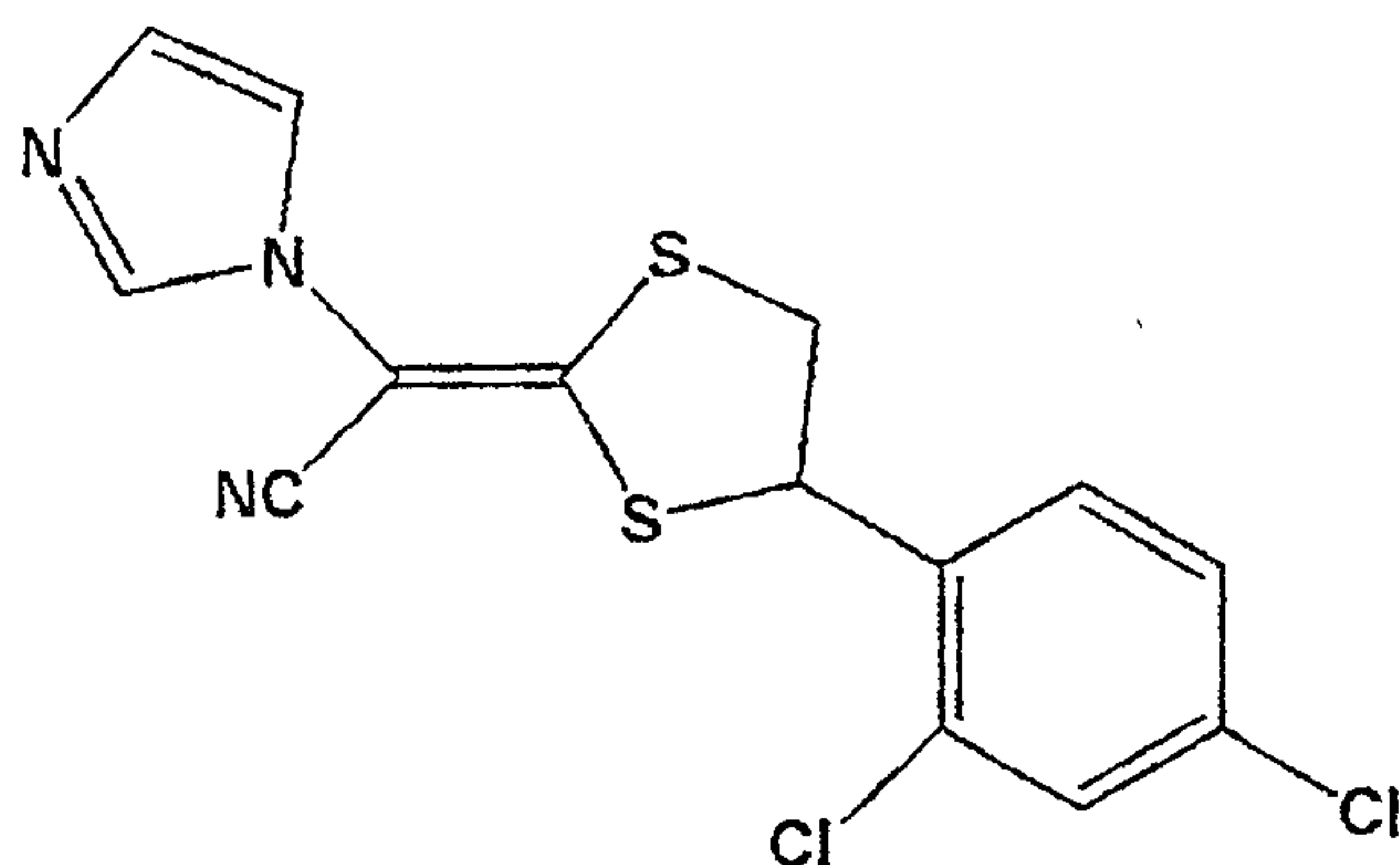
According to the present invention, it becomes possible to provide a pharmaceutical composition for external use having an excellent penetration-absorption of luliconazole and/or a salt thereof.

72689-179

CLAIMS:

1. A pharmaceutical composition for external use, comprising:

- 5 (i) luliconazole represented by the following structural formula (1) and/or a salt thereof; wherein the composition comprises luliconazole in an amount of 0.5 to 15 % by mass;



Structural formula (1)

- 10 (ii) 1 to 10 % by mass lactic acid and/or salt thereof; and

(iii) ethanol, wherein the concentration of ethanol is 50 to 90 % by mass.

2. The pharmaceutical composition for external use according to claim 1, wherein the ratio of lactic acid to
15 luliconazole is 0.1 to 10.

3. The pharmaceutical composition for external use according to claim 1 or 2, wherein the ratio of lactic acid to luliconazole is 0.5 to 5.

72689-179

4. The pharmaceutical composition for external use according to any one of claims 1 to 3, wherein the ratio of lactic acid to luliconazole is 0.8 to 2.

Application number / numéro de demande: JP 2006 / 319705

Figures: 1, 2, 3, 4, 5, 6

Pages: 38, 39, 40, 41, 42, 43

Unscannable item(s)

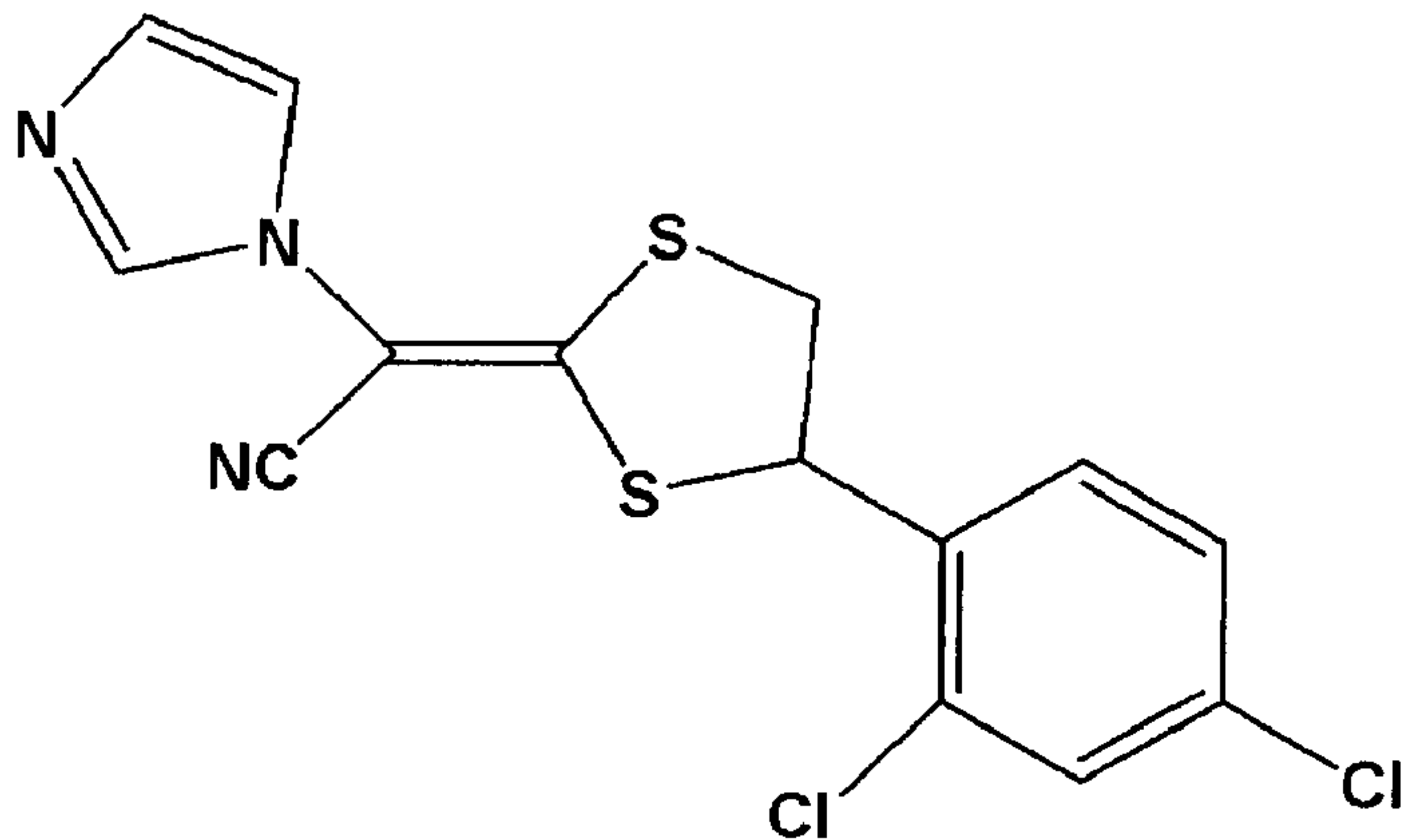
received with this application

To inquire if you can order a copy of the unscannable items, please visit the
CIPO WebSite at [HTTP://CIPO.GC.CA](http://CIPO.GC.CA)

Item(s) ne pouvant être balayés

Documents reçus avec cette demande ne pouvant être balayés.

Pour vous renseigner si vous pouvez commander une copie des items ne
pouvant être balayés, veuillez visiter le site web de l'OPIC au [HTTP://CIPO.GC.CA](http://CIPO.GC.CA)



Structural formula (1)