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EDIFICIO
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SUPERINDUSTRIA Y COMERCIO

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Trámite : 002 PATENTES D I REGISTRO/ 538 PETICION

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

TRÁMITE : 002

EVENTO : 001

ACTUACIÓN : 538

Referencia : Expediente No. 00-097.424
Asunto : Solicitud de patente para: USO DE AZOLES PARA LA PREVENCIÓN DEL CANCER DE PIEL
Solicitante : BAYER AKTIENGESELLSCHAFT
Fecha de solicitud : 22 de diciembre de 2000
Publicada en : la Gaceta No. 525 del 28 de febrero de 2003

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo No. 03-59,891 por valor de \$335.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 41687 del 24 de diciembre de 2002.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo, para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Bogotá, 27 AGO. 2003
Señora Jefe,


EMILIO FERRERO
T.P.A. No. 31.929

COLO 00698 801 142 2
MRE/JFR/ID-001366/WPCL0698 NIT. 860.041.367-3

60 58

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00097424 00000004 Folios: 2
Fecha (AMD): 2003-08-27 16:47:09
NIT : 80017606 Trámite : 002 PATENTES D 1 REGISTRO/ 530 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 03 - 59,891
FECHA : AGOSTO 23 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	15534375	25/08/2003	72,770,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	30005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	335,000.00
		TOTAL :	\$ 335,000.00

SOM: TRESCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Colo 00698-801-142-2

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 00-97424

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 525, DE

FECHA 28 DE FEBRERO DE 2003, EL TERMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL 29 DE MAYO DE 2003.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud calga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ **NO** X _____

United States Patent

Buchel et al.

[15] 3,691,192

[45] Sept. 12, 1972

[34] AN N-TRITYL-IMIDAZOLE

[72] Inventors: Karl-Helm Buchel, Wuppertal-Eilberfeld; Erik Regel, Wuppertal-Cronenberg; Ferdinand Growe, Burscheid; Hans Scholpflug; Holmst Kampers, both of Leverkusen, all of Germany

[73] Assignee: Farbenfabriken Bayer Aktiengesellschaft, Leverkusen, Germany

[22] Filed: May 15, 1970

[21] Appl. No.: 37,841

Related U.S. Application Data

[62] Division of Ser. No. 789,601, Jan. 7, 1969, abandoned.

[30] Foreign Application Priority Data

Jan. 29, 1968 Germany.....P 16 70 976.5

[52] U.S. Cl. 260/309, 260/465 F, 260/465 G, 260/609 E, 260/618 R, 260/645, 260/646, 260/649 R, 424/273

[51] Int. Cl. C07d 49/36

[58] Field of Search.....260/309

[56] References Cited

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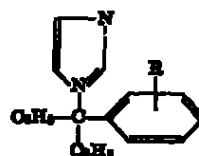
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Giesemann et al. II Chem. Berichte Vol. 92, pages 92-8 (1959). QD1.D4
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Primary Examiner—Natalie Trouse
Attorney—Jacobs & Jacobs

[57] ABSTRACT

N-trityl-imidazoles of the formula:

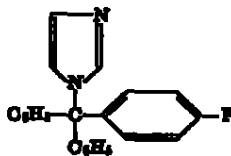


in which R is selected from the group consisting of halo, nitro, cyano, alkyl of one to three carbon atoms, alkoxy of one to three carbon atoms alkylmercapto of one to three carbon atoms and fluoro-substituted alkyl of one to two carbon atoms, are effective against fungi pathogenic to plants.

1 Claim, No Drawings

ing 167 g of crude 1-[(p-chlorophenyl)-(biphenyl)-methyl]-imidazole, m.p. 125° C. By recrystallization from 200 ml benzene and 100 ml ligroin, 115 g (= 71 percent of the theory) of pure 1-[(p-chlorophenyl)-(bis-phenyl)-methyl]-imidazole of m.p. 140° C are obtained.

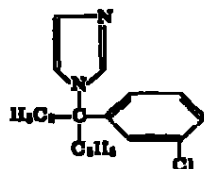
EXAMPLE 7



34 g (0.5 mol) imidazole are dissolved at room temperature, with stirring, in a solution of 148.25 g (0.5 mol) of (p-fluorophenyl)-(diphenyl)-methyl chloride in 500 ml acetonitrile. Following this, 51 g (0.5 mol) triethylamine are added dropwise; triethylamine hydrochloride separates immediately upon heating. For completion of the reaction, the mixture is heated at 50° C for 3 hours. After cooling, the reaction mixture is stirred together with 1 liter of benzene and washed salt-free with water. The benzene solution is dried over anhydrous sodium sulfate, filtered and concentrated by evaporation; giving 148 g of crude 1-[(p-fluorophenyl)-(bisphenyl)-methyl]-imidazole of m.p. 146° C (= 91 percent of the theory). By recrystallization from 300 ml benzene and 50 ml ligroin, the m.p. rises to 148° C.

The (p-fluorophenyl)-(diphenyl)-methyl chloride used as starting material can be prepared as follows: 174.9 g (1 mol) p-fluoro-bromobenzene in 175 ml ether are slowly added dropwise to 24.3 g (1 gram-atom) magnesium in 300 ml ether. After all the magnesium is dissolved, a solution of 182 g (1 mol) benzophenone in 500 ml ether is added dropwise. The magnesium salt of the alcohol separates from the initially deep-violet solution towards the end of the reaction. By washing with 10 percent ammonium chloride solution, the alcohol is obtained which, without isolation, is immediately further processed by dissolving it in 1 liter of benzene, adding 50 g of calcium chloride and introducing hydrogen chloride gas until saturation. After filtration and removal of the solvent, the resulting crystal slurry is vigorously suction filtered and the crystals obtained are washed with petroleum ether. 205 g (= 69 percent of the theory) of (p-fluorophenyl)-(diphenyl)-methyl chloride of m.p. 88° C are obtained.

EXAMPLE 8



27.2 g (0.4 mol) imidazole and 62.8 g (0.2 mol) of (m-chlorophenyl)-(diphenyl)-methyl chloride are heated to 80° C for 4 hours in 150 ml of dry acetonitrile and 50 ml dimethyl formamide. The solvent is then drawn off and the residue is digested with water to remove the imidazole hydrochloride. The residue is taken up in methylene chloride, dried over sodium sulfate, and the viscous oil remaining behind after the distilling off of the solvent is recrystallized from cyclohexane. 52 g (75 percent of the theory) of 1-[(m-chlorophenyl)-(biphenyl)-methyl]-imidazole of m.p. 101° C are obtained.

In analogous manner, the following compounds of the general formula (I) above are prepared:

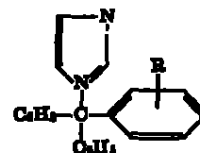
Compound	R	m.p. °C
(7.)	o-Cl	140
(8.)	m-Cl	156
(9.)	o-OCH ₃	130
(10.)	p-Br	152
(11.)	p-SCH ₃	142
(12.)	p-CH ₃	130
(13.)	o-F	185
(14.)	m-F	174
(15.)	p-NO ₂	160-170
(16.)	p-CN	164

It will be realized by the artisan that all of the foregoing compounds contemplated by the present invention possess the desired strong fungicidal properties, with regard to a broad spectrum of activity, as well as a comparatively low toxicity toward warm-blooded creatures and a concomitantly low phytotoxicity, enabling such compounds to be used with correspondingly favorable compatibility with warm-blooded creatures and plants for more effective control and/or elimination of fungi by application of such compounds to such fungi and/or their habitat.

It will be appreciated that the instant specification and examples are set forth by way of illustration and not limitation, and that various modifications and changes may be made without departing from the spirit and scope of the present invention.

What is claimed is:

1. An N-trityl-imidazole of the formula:



in which R is o-methyl.

* * * * *

[34] 4-[4-[[2-(HALOPHENYL)-2-(1H-TETRAZOL-5-YLMETHYL)-1,3-DIOXOLAN-4-YL]METHOXY]PHENYL]-PIPERAZINE-1-CARBOXYLIC ACIDS HAVING ANTIMYCOTIC ACTIVITY

[75] Inventors: Helmut Schickaneder, Eckental; Rolf Hertz, Schwabach; Hartmut Verga, Nuremberg; Heidrun Engler, Cadolzburg; Kurt H. Ahrens, Nuremberg, all of Fed. Rep. of Germany

[73] Assignee: Heumann Pharma GmbH & Co., Nuremberg, Fed. Rep. of Germany

[21] Appl. No.: 69,159

[22] Filed: Jul. 2, 1987

[30] Foreign Application Priority Data

Jul. 7, 1986 [DE] Fed. Rep. of Germany 3621791

[51] Int. Cl.⁴ A61K 31/41; A61K 31/335; A61K 31/415; A61K 31/425

[52] U.S. Cl. 514/252; 544/366; 544/367; 544/370

[58] Field of Search 544/367, 366, 30; 514/252

[56] References Cited

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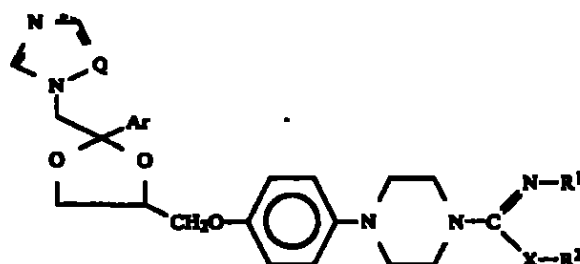
Primary Examiner—Donald G. Dams

Assistant Examiner—C. Shen

Attorney, Agent, or Firm—Burns, Doane, Swecker & Mathis

[57] ABSTRACT

The invention relates to new 1,4-piperazine compounds corresponding to the following general formula



which show improved antimycotic activity in relation to the known compounds miconazol and ketoconazol.

6 Claims, No Drawings

[34] CANCER TREATMENTS

[75] Inventors: Jose Halperin, Brookline; Carlo Brugnara, Newton Highlands, both of Mass.

[73] Assignee: President and Fellows of Harvard College, Cambridge, Mass.

[21] Appl. No.: 18,828

[22] Filed: Feb. 18, 1993

[31] Int. Cl.⁶ A61K 31/415

[32] U.S. Cl. 514/405; 514/385; 514/396

[38] Field of Search 514/396, 405, 514/385

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(List continued on next page.)

Primary Examiner—Theodore J. Crites

Attorney, Agent, or Firm—Edward R. Gates; Wolf, Greenfield & Sachs, P.C.

[57] ABSTRACT

The Applicant has identified a particular class of imidazoles that inhibit nonprostate cancer cell proliferation. These imidazoles can be used to beneficially treat a variety of cancers. The imidazoles can be administered in a variety of formulations, including long-term sustained release implants and anti-cancer cocktails.

26 Claims, 2 Drawing Sheets

CANCER TREATMENTS

FIELD OF THE INVENTION

The invention relates in general to the field of cancer and more particularly to the use of imidazoles that inhibit the Ca^{++} activated potassium channel in arresting non-prostate cancer cell proliferation.

BACKGROUND OF THE INVENTION

It has been said that one-third of all people in the United States will develop cancer. Although remarkable progress has been made in understanding the biological basis of and in treating cancer, cancer remains second only to cardiac disease as the main cause of death in the United States.

Chemotherapy is an important tool in treating cancer. In 1945, there was but a single agent known to be an effective antineoplastic drug. Today, there are more than 50. Nevertheless, the search for effective antineoplastic drugs and drug combinations has, if anything, intensified in an effort to find even more effective agents for treating the myriad of cancers that threaten and take the lives of so many.

Imidazoles are synthetic antifungal agents that are used both topically and systemically. Indications for their use include ringworm, tinea versicolor and mucocutaneous candidiasis. These compounds are believed to act by inhibiting ergosterol synthesis in the fungal cell wall, and when given topically, may cause direct damage to the cytoplasmic membrane.

The fungi comprise five widely differing classes of primitive flora, and the variation in cell physiology and biochemistry are extreme. As a result, most antifungal agents have a very narrow spectrum of antifungal activity.

Various imidazoles have been suggested as treatments for prostate cancer. The only one known to the applicants to have been tested is ketoconazole. Ketoconazole is an antifungal agent that, in high doses, inhibits testicular and adrenal synthesis of steroid hormones, including testosterone. The ability of ketoconazole to block steroid synthesis has prompted its use in the treatment of advanced prostate carcinoma because prostate cancer cells are highly dependent upon testosterone. The major sites of action appear to be in the inhibition of 17-20 desmolase, partial blockade of 17-hydroxylase and marked inhibition of 21- and/or 11-hydroxylase, all major enzymes of the androgenic hormone synthetic pathways.

In the recent past, newer methods of androgen ablation for the treatment of metastatic prostate carcinoma have been developed as alternatives to the standard forms of therapy: oral estrogens and surgical castration. Luteinizing hormone-releasing hormone (LHRH) analogs, potent inhibitors of testosterone production, have recently emerged as major players in the long term treatment of advanced prostate cancer. In contrast, ketoconazole has been found to be excellent for short-term usage prior to bilateral orchiectomy and when prompt therapeutic response is needed but orchiectomy cannot be performed. In high doses, ketoconazole causes castrate levels of testosterone within 24 to 48 hours; therefore, it is extremely useful in the initial medical treatment of patients with metastatic prostate cancer who need a prompt therapeutic response. Thus, ketoconazole has been used as a hormonal adjuvant for prostate cancer treatment; it reduces plasma testosterone to castration levels. Ketoconazole, as will be described below, is not useful for inhibiting proliferation of the nonprostate cancer cells tested.

SUMMARY OF THE INVENTION

The Applicant has identified a particular class of imidazoles that inhibit nonprostate cancer cell proliferation. These imidazoles can be used to beneficially treat various cancers.

According to one aspect of the invention, a method for treating cancer is provided. An imidazole is administered to a subject that has a nonprostate cancer. The imidazole is an inhibitor of the Ca^{++} activated potassium channel and is an inhibitor of nonprostate cancer cell proliferation. The methods are particularly useful in connection with the treatment of cancers that are nonhormone-sensitive. Preferred imidazoles are clotrimazole, miconazole and econazole.

According to another aspect of the invention, a method for inhibiting the growth of nonprostate cancer cells is provided. The cells of a species are contacted with an imidazole that inhibits the Ca^{++} activated potassium channel of erythrocytes of the species. Such methods may be in vivo or ex vivo.

Preferably, the cancer cells are in a preparation, tissue, subject or environment that is substantially free of fungi. As such, the treatment typically is for subjects that are otherwise free of indications for the preferred imidazoles.

According to another aspect of the invention, a sustained release implant containing an imidazole as described above is provided. The implant is constructed and arranged for the long-term delivery of the imidazole when implanted in vivo. Still another aspect of the invention is a cocktail of anti-cancer agents, including an imidazole as described above.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph illustrating the ability of clotrimazole to inhibit nonprostate cancer cell proliferation.

FIG. 2 is a graph showing that clotrimazole inhibits DNA synthesis in a dose-dependent fashion.

FIG. 3 is a graph comparing the effect upon cell-proliferation of a variety of drugs.

FIG. 4 is a graph comparing the effect upon the Ca^{++} activated potassium channel of the same drugs tested in connection with FIG. 3.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention is used in connection with treating non-prostate cancers. Nonprostate cancers include: biliary tract cancer; brain cancer, including glioblastomas and medulloblastomas; breast cancer; cervical cancer; choriocarcinoma; colon cancer; endometrial cancer; esophageal cancer; gastric cancer; hematological neoplasms, including acute lymphocytic and myelogenous leukemia, multiple myeloma, AIDS associated leukemias and adult T-cell leukemia lymphoma; intraepithelial neoplasms, including Bowen's disease and Paget's disease; liver cancer; lung cancer; lymphomas, including Hodgkin's disease and lymphocytic lymphomas; neuroblastomas; oral cancer, including squamous cell carcinoma; ovarian cancer, including those arising from epithelial cells, stromal cells, germ cells and mesenchymal cells; pancreas cancer; rectal cancer; sarcomas, including leiomyosarcoma, rhabdomyosarcoma, liposarcoma, fibrosarcoma and osteosarcoma; skin cancer, including melanoma, Kaposi's sarcoma, basocellular cancer and squamous cell cancer; testicular cancer, including germinal tumors (seminoma, non-seminoma (teratomas, choriocarcinomas)), stromal tumors and germ cell tumors; thyroid cancer, including thyroid adenocarcinoma and med-

3

ular carcinoma; and renal cancer including adenocarcinoma and Wilms tumor.

Proliferation of cancer cells is a main pathological feature of cancer. Proliferation of prostate cancer cells can be hormone (testosterone)-dependent; that is, proliferation of prostate cancer cells can be inhibited or arrested by eliminating the presence of testosterone, such as by castration. As discussed above, ketoconazole has been tested as an anti-cancer agent for prostate cancer because of its ability to block testosterone synthesis. Ketoconazole, on the other hand, was ineffective in inhibiting the growth of the non-prostate cancer cells tested by the applicants.

The imidazoles useful in this invention are believed to have a different mechanism of action and are useful in inhibiting and arresting the growth of cancer cells that do not depend upon the presence of hormones for proliferation or nonproliferation (i.e., nonhormone-dependent cancer.)

The compounds useful in the present invention are imidazoles that inhibit the Ca^{++} activated potassium channel. Such imidazoles are either known to those of ordinary skill in the art or can be identified without undue experimentation using established tests routinely employed by those of ordinary skill in the art. One such test involves human erythrocytes and is described in the examples, below. When using this test, it is desirable to select imidazoles that are inhibitory to an extent of at least about 75%.

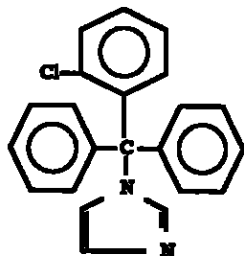
The imidazoles of the invention also inhibit nonprostate cancer cell proliferation. Inhibition of such proliferation may be tested without undue experimentation using established tests routinely employed by those of ordinary skill in the art (See e.g. examples below.) The imidazoles used in the methods of this invention preferably are inhibitory of non-prostate cancer cell proliferation in such tests to an extent of at least about 75%.

It was not expected that inhibitors of the Ca^{++} activated potassium channel would inhibit nonprostate cancer cell proliferation. Other specific inhibitors of the Ca^{++} activated potassium channel (such as charybdotoxin, calitoxin and Iberotoxin) do not inhibit proliferation of nonprostate cancer cells. Moreover, inhibitors of other transport systems that are activated by mitogens, such as ouabain (highly specific inhibitor of the Na/K pump) and amiloride (inhibitor of Na/H exchange) do not inhibit cell proliferation. Thus, the results obtained by the applicants are surprising.

Without limiting the invention to the use of the specific compounds listed, the following is a list of preferred compounds and well-characterized salts thereof useful in the methods of the invention.

Chlorimazole

1H-Imidazole, 1-[2-(4-chlorophenyl)phenylmethyl]-, Lotilan (Schering); Mycolan (Miles)

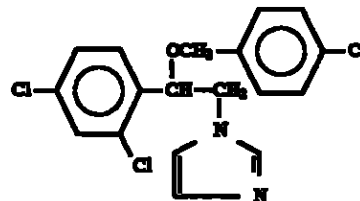


1-(o-Chloro-o,p-dichlorophenyl)imidazole [2533-75-1] $\text{C}_{10}\text{H}_7\text{ClN}_2$ (344.84).

4

-continued Benzazole

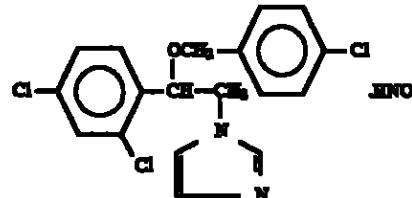
1H-Imidazole, (±)-1-[2-[(4-chlorophenyl)methyl]-2-(2,4-dichlorophenyl)ethyl]-, meconazole, Meconazole (Squibb)



(±)-1-[2,4-Dichloro-β-[(p-chlorobenzyl)methyl]phenethyl]imidazole meconazole [68797-31-9] $\text{C}_{18}\text{H}_{15}\text{Cl}_3\text{N}_2\text{O}$.

Benzazole Nitrate

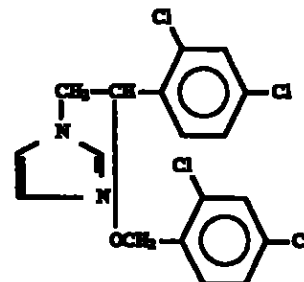
1H-Imidazole, (±)-1-[2-[(4-chlorophenyl)methyl]-2-(2,4-dichlorophenyl)ethyl]-, meconazole, Meconazole (Squibb)



(±)-1-[2,4-Dichloro-β-[(p-chlorobenzyl)methyl]phenethyl]imidazole meconazole [68797-31-9] $\text{C}_{18}\text{H}_{15}\text{Cl}_3\text{N}_2\text{O.HNO}_3$ (480.70).

Miconazole

1H-Imidazole, 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methyl]ethyl]-, Miconazole (Roche)



1-[2,4-Dichloro-β-[(2,4-dichlorobenzyl)methyl]phenethyl]imidazole [22916-47-8] $\text{C}_{18}\text{H}_{12}\text{Cl}_4\text{N}_2\text{O}$ (416.12).

Miconazole Nitrate

Miconazole (Roche)
[22932-87-7] $\text{C}_{18}\text{H}_{12}\text{Cl}_4\text{N}_2\text{O.HNO}_3$ (479.15).

The above imidazoles are well recognized, pharmacologically characterized, and licensed for use by the FDA today either as antimycotic agents or antiprotozoal agents. As such, established and empirically documented parameters regarding their limited toxicity and their useful dosages are well described in the scientific and medical literature.

The imidazoles used in the methods of the invention may be administered per se (neat) or in the form of a pharmaceutically acceptable salt. When used in medicine, the salts should be both pharmacologically and pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare the free active compound or pharmaceutically acceptable salts thereof. Pharmacologically and pharmaceutically acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric,

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maleic, acetic, salicylic, p-toluenesulfonic, tartaric, citric, methanesulphonic, formic, malonic, succinic, naphthalene-2-sulphonic, and benzenesulphonic. Also, pharmaceutically acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts of the carboxylic acid group. Thus, the present invention involves the use of pharmaceutical formulations which comprise certain imidazoles together with one or more pharmaceutically acceptable carriers and optionally other therapeutic ingredients. The carrier(s) and other ingredients of course must be pharmaceutically acceptable.

Analogous of the foregoing compounds that act as functional equivalents also are intended to be embraced as equivalents and within the scope of the invention.

A subject as used herein means: Humans, primates, horses, cows, pigs, sheep, goats, dogs, cats and rodents.

A variety of administration routes are available. The particular mode selected will depend, of course, upon the particular drug selected, the particular condition being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces therapeutic levels of the imidazoles of the invention without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, topical, nasal, transdermal or parenteral (e.g. subcutaneous, intramuscular and intravenous) routes. Transdermal or topical formulations may be particularly suitable, or even preferred, for certain cancers such as basal cell carcinoma and Kaposi's sarcoma. Formulations for oral administration include discrete units such as capsules, tablets, lozenges and the like. Other routes include intrathecal administration directly into spinal fluid and direct introduction onto, in the vicinity of or within cancer cells.

The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing the active imidazole into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the imidazole into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the imidazole, in liposomes or as a suspension in an aqueous liquor or non-aqueous liquid such as a syrup, an elixir, or an emulsion.

Compositions suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the imidazole, which is preferably isotonic with the blood of the recipient. This aqueous preparation may be formulated according to known methods using those suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in polyethylene glycol and lactic acid. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

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Other delivery systems can include sustained release delivery systems. Preferred sustained release delivery systems are those which can provide for release of the imidazoles of the invention in sustained release pellets or capsules. Many types of sustained release delivery systems are available. These include, but are not limited to: (a) erosional systems in which the imidazole is contained in a form within a matrix, found in U.S. Pat. Nos. 4,452,775 (Kent), 4,667,014 (Nester et al.); and 4,748,024 and 5,239,660 (Leonard) and (b) diffusional systems in which an active component permeates at a controlled rate through a polymer, found in U.S. Pat. Nos. 3,832,252 (Higuchi et al.) and 3,854,480 (Zaffaroni). In addition, a pump-based hardware delivery system can be used, some of which are adapted for implantation.

Use of a long-term sustained release implant may be particularly suitable for treating certain cancers, including solid tumors. "Long term" release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the imidazole for at least 30, and preferably 60 days. Such implants can be particularly useful in treating solid tumors by placing the implant near or directly within the tumor, thereby affecting localized, high-doses of the imidazole. Such implants can be especially useful in delivering imidazoles that are not successfully ingested, or that do not pass biological barriers, such as the blood/brain barrier. They also can be used to avoid undesirable emulsification, such as when brain tumors are being treated. Long-term sustained release implants are well known to those of ordinary skill in the art and include some of the release systems described above.

Oral administration for many nonprostate cancers will be preferred because of the convenience to the patient, although topical and localized sustained delivery may be even more desirable for certain treatment regimens.

The imidazoles, when used *in vivo*, are administered in therapeutically effective amounts. A therapeutically effective amount means that amount necessary to inhibit the progression of or halt altogether progression of the particular nonprostate cancer being treated. Such amounts will depend, of course, on the particular condition being treated, the severity of the condition, and individual patient parameters including age, physical condition, size, weight and concurrent treatment. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is preferred generally that a maximum dose be used, that is, the highest safe dose according to sound medical judgment. It will be understood by those of ordinary skill in the art, however, that a patient may insist upon a lower dose or tolerable dose for medical reasons, psychological reasons or for virtually any other reasons.

Generally, daily oral doses of active compound will be from about 0.01 milligrams/kg per day to 1000 milligrams/kg per day. Small doses (0.01-1 mg) may be administered initially, followed by increasing doses up to about 1000 mg/kg per day. In the event that the anti-cancer response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent patient tolerance permits. Multiple doses per day are contemplated to achieve appropriate systemic levels of compounds.

The imidazoles useful in the invention may be delivered in the form of anti-cancer cocktails. An anti-cancer cocktail is a mixture of any one of the imidazoles useful with this invention with another anti-cancer drug and/or supplement.

tery potentiating agent. The use of cocktails in the treatment of cancer is routine. In this embodiment, a common administration vehicle (e.g., pill, tablet, implant, injectable solution, etc.) would contain both the imidazole useful in this invention and the anti-cancer drug and/or supplementary potentiating agent.

Anti-cancer drugs are well known and include: Aminoglutethimide; Asparaginase; Bleomycin; Busulfan; Carboplatin; Carmustine (BCNU); Chlorambucil; Cisplatin (cis-DDP); Cyclophosphamide; Cytarabine HCl; Dacarbazine; Dactinomycin; Daunorubicin HCl; Doxorubicin HCl; Estramustine phosphate sodium; Etoposide (V16-213); Floxuridine; Fluorouracil (5-FU); Flutamide; Hydroxyurea (hydroxycarbamide); Ifosfamide; Interferon Alfa-2a, Alfa 2b; Leuprolide acetate (LHRH-releasing factor analogue); Lomustine (CCNU); Mechlorethamine HCl (nitrogen mustard); Melphalan; Mercaptopurine; Meclizine; Methotrexate (MTX); Mitomycin; Mitotane (o. p'-DDD); Mitoxantrone HCl; Octreotide; Plicamycin; Procarbazine HCl; Streptozocin; Tamoxifen citrate; Thioguanine; Thiopeta; Vinblastine sulfate; Vincristine sulfate; Vinasaric (m-AMSA); Azacitidine; Hexamethylmelamine (HMM); Interleukin 2; Mitoguanos (methyl-GAG; methyl glyoxal bis-guanyldihydrazone; MGBG); Pentostatin; Semustine (methyl-CCNU); Teniposide (VM-26) and Vinorelbine sulfate.

Supplementary potentiating agents likewise are well characterized and include: Tricyclic anti-depressant drugs (e.g., imipramine, desipramine, amitriptyline, clomipramine, trimipramine, doxepin, nortriptyline, protriptyline, amoxapine and maprotiline); non-tricyclic anti-depressant drugs (e.g., sertraline, trazodone and citalopram); Ca^{++} antagonists (e.g., verapamil, nifedipine, nitrendipine and caroverine); Calmodulin inhibitors (e.g., prenylamine, trifluoroperazine and clomipramine); Amphoteracin (e.g., Tween 80 and per-heardline maleate); Triperanol analogues (e.g., tamoxifen); antiarrhythmic drugs (e.g., quinidine); antihypertensive drugs (e.g., reserpine); and Thiol depletors (e.g., buthionine and sulfoximine).

The imidazoles of the invention, when used in cocktails, are administered in therapeutically effective amounts. A therapeutically effective amount will be determined by the parameters discussed above; but, in any event, is that amount which establishes a level of the drug in the area of the tumor which is effective in inhibiting the tumor growth.

EXAMPLES

Materials

Abbreviations: ChTX, Charybdotoxin; CLT, clotrimazole; ECZ, econazole; MCZ, miconazole; FCZ, fluconazole; MRTZ, metronidazole; IbTX, ibuprofen; KTX, kalitoxin; DIDS, di-isothiocyano-disulfonate stilbene; hemoglobin concentration; MCHC, mean corpuscular hemoglobin concentration; MOFS, 3-[N-morpholino]propanesulfonic acid.

Drugs and Chemicals

Synthetic charybdotoxin (ChTX) was purchased from Peptides International (Louisville, Ky.). A23187 was purchased from Calbiochem-Behring (LaJolla, Calif.). Fluconazole was provided by Pfizer Inc., Groton, Conn., disulfonate acid (MOFS), clotrimazole (CLT), miconazole, econazole, metronidazole, and all other drugs and chemicals were purchased from Sigma Chemical Co. (St. Louis, Mo.) and Fisher Scientific Co. (Fair Lawn, N.J.), and the radioisotope ^{3}H from Dupont (Billericia, Mass.).

Assays for Cell Proliferation

DNA synthesis assessed by the uptake of $[3H]$ thymidine: Cells are grown in either 48 or 96 wells plates (Costar,

Cambridge, Mass.) at 10^4 and 0.8×10^5 cells per well, respectively, and grown in Dubelco's modified Eagle's medium (DMEM, Gibco, Grand Island, N.Y.) supplemented with 10% heat-inactivated calf serum; they are kept at $37^\circ C$. in 5% CO_2 . When they reach confluence, usually between 3 and 4 days, the medium is replaced with DMEM 0.5% serum to make them quiescent, and mitogenesis assays are performed 24 hours later.

Quiescent cells are exposed to a mitogenic stimulus, such as 10% serum, PDGF (Sigma Co. St. Louis, Mo.), bFGF (Upstate Biotechnology, Lake Placid, N.Y.), or other appropriate mitogen according to the cell line, and 3 hours later $1 \mu Ci/ml$ of $[3H]$ thymidine (Dupont, Billericia, Mass.) is added to the wells, and the cells maintained at $37^\circ C/5\% CO_2$ for additional 21 hours. Then the cells are washed 3 times with DMEM medium and the acid-precipitable radioactivity is extracted with cold 10% TCA (Sigma, Co.). After neutralization with 0.3N NaOH (Sigma Co.), aliquots are counted in a Packard Tri-Carb Scintillation counter (Packard Instrument, Downer's Grove, Ill.).

Measurement of cell density in culture plates: Cells of a specific test cell line are seeded at precisely the same low density in culture plates and incubated for approximately 12 hours in DMEM 10% serum, or other culture medium depending on the cell line tested. After 12 hours, the test drug, for example clotrimazole $10 \mu M$, is added to the cell medium of one plate and a similar amount of only the carrier of the drug, for example ethanol $10 \mu l$, to another plate. After 48 to 74 hours, the cell density in control (ethanol) and experimental (clotrimazole) plates is assessed under a light inverted microscope, by measuring the surface of the culture plate covered by the cell monolayer. Alternatively, the cells can be detached from the plate by incubation with trypsin (Sigma, Co.) 50% (v/v) in ethylene diaminetetraacetic acid (EDTA; Sigma, Co.); then the cells are counted in an hemocytometer chamber (Fisher, Pittsburgh, Pa.).

Assays for Inhibitors of Ca^{++} Activated K Channel

Ca^{++} -sensitive K^+ channels have wide distribution among cells, including the human red cell where they were originally discovered and which is the most commonly utilized assay system for activators and inhibitors of the channel for the following reasons: they are readily available, can be easily manipulated in the laboratory, and transport assays can be accurately standardized by reading the hemoglobin concentration of a red cell suspension.

Preparation of Human Red Blood Cells: Blood is collected in heparinized tubes and centrifuged in a Sorvall centrifuge (RB 5B, Du Pont Instruments, Newtown, Conn.) at $5^\circ C$. for 10 minutes at 3000 g. Plasma and buffy coat are carefully removed and the cells washed four times with a washing solution containing 150 mM choline chloride (Sigma Co.), 1 mM $MgCl_2$ (Sigma Co.), 10 mM Tris-MOPS (Sigma, Co.), pH 7.4 at $4^\circ C$ (CWS). An aliquot of cells is then suspended in an approximately equal volume of CWS, and from this original cell suspension hematocrit (Hct) and hemoglobin (optical density at 540 nm) are determined.

Methods to Test Inhibitors of the Ca^{++} Activated K: To test inhibitors of the Ca^{++} activated K channel, the channel is activated using the calcium ionophore A23187 (Calbiochem).

By Atomic Absorption Spectrometry: Washed human erythrocyte are suspended at an hematocrit-1% in CWS containing 0.150 mM $CaCl_2$ (Sigma Co) Aliquots of 1 ml are removed at 0, 3 and 5 minutes, layered on top of 0.3 ml of the oil n-butyl phthalate (Fair Lane, N.J.) placed in an Eppendorf microtube (Fisher) and then centrifuged in a micro centrifuge for 20 seconds. At time 5.30 minutes,

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ionophore A23187 (1 μM final concentration) is added and samples removed and spin down through phthalate at times 6, 7, 8 and 9 minutes. The supernatant on top of the oil layer is removed and its K^+ concentration is measured by atomic absorption spectrometry using a Perkin Elmer model 5000 spectrometer (Perkin Elmer Corp., Norwalk, Conn.). The efflux of K^+ (nmol/l cells/h) in the absence and presence of the inhibitor is calculated from the slope of the curves relating the K^+ concentration in the supernatants (nmol/l cells) vs. time (min.).

By radioisotopic measurement of ^{86}Rb influx. The incubation medium is the same but contains 2 mM KCl and 1 $\mu\text{Ci}/\text{ml}$ of the radioactive tracer ^{86}Rb . After spinning the samples through the phthalate layer, the tubes are rapidly frozen (-80°C) by immersion in methanol-dry ice, the tips of the tubes containing the packed red cells cut, and counted in a Packard Gamma Counter.

EXAMPLE 1

The inhibitory effect of clotrimazole (CLT) on cell proliferation was assessed in cancerous cells. Quiescent human colon adenocarcinoma and human lung adenocarcinoma cells were stimulated with 5% fetal calf serum and synthesis of DNA was assessed by the incorporation of $[^3\text{H}]\text{thymidine}$ measures 24 hours later. As shown in FIG. 1, 10 μM CLT completely inhibited DNA synthesis in both cancer cell lines. The effect was not due to a toxic, non-specific, effect because it was reversed by removing CLT and re-stimulating the cells with 5% fetal calf serum (FIG. 1).

EXAMPLE 2

Dose response inhibitors of DNA synthesis by clotrimazole was tested using rat vascular smooth muscle cells as described above. Clotrimazole was tested at concentrations of 0.001 μM , 0.1 μM , 1 μM and 10 μM . Cells were stimulated using 5 μM bFGF. Inhibition was dose dependent, with 45% inhibition at 1 μM and complete inhibition at 10 μM . The ID_{50} was about 1.5 μM . (FIG. 2)

EXAMPLE 3

Primary human sarcomas rhabdomyosarcoma and liposarcoma: Fresh human cancer specimens were obtained from human subjects undergoing a surgical procedure; the tumors were treated with collagenase to dissociate the cells which were then seeded at low density (1×10^3 in small culture chambers containing hybridoma grade culture medium supplemented with 5% fetal calf serum; after 12 hrs., when the cells were attached to the surface of the culture chambers, CLT (10 μM) or carrier (ethanol) were added (triplicate chambers). After 48 hours cell growth was assessed by optic microscopy calculating the surface of the culture flask covered by the cell monolayer. The growth of both sarcoma cells were completely arrested by CLT. More than 95% inhibition was obtained with 10 μM CLT.

EXAMPLE 4

Other antimycotics were tested for their inhibition of bFGF-stimulated DNA synthesis in the primary human sarcoma cells of Example 3. As shown in FIG. 3, at a concentration of 10 μM , 3 compounds, CLT, econazole (ECZ) and micronazole (MCZ) inhibited DNA synthesis. The order of inhibitory potency was CLT more potent than ECZ, and ECZ more potent than MCZ. In contrast, other inhibitors of the Ca^{++} activated K channel, namely Charybdotoxin, kalitoxin and iberiotoxin, also failed to inhibit DNA synthesis.

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EXAMPLE 5

The inhibitory effect of (CLT) on the Ca^{++} activated K channel of human erythrocytes was assessed in the presence of 60 μmol A23187/L cell and 100 μM CaCl_2 . CLT markedly inhibited the Ca^{++} activated ^{86}Rb influx and K efflux. Mean values of ID_{50} (calculated with Dixon plot analysis) was 143 ± 60 nM ($n=3$).

Other antimycotics were tested for their inhibition of the Ca^{++} activated ^{86}Rb influx human erythrocytes. The order of inhibitory potency was clotrimazole more than econazole; and both of these were more than micronazole. There was no inhibition by fluconazole, ornidazole and thidazole, 2 related compounds, and only marginal with nitroimidazole a member of the nitroimidazole group (FIG. 4).

EXAMPLE 6

Inhibition of tumor growth in vivo:

The efficacy of CLT was studied in inhibiting the growth of adenocarcinomas in rats. Animals were inoculated with LD100 doses of one tumor line and were randomly allocated to groups of five animals, which received in different doses of carrier alone or CLT (20, 50, 100 and 200 mg/kg) dissolved in peanut oil and administered by mouth with a special device adapted to a plastic catheter. Tumors were measured by size and weight on a daily basis, and growth rates were calculated. Nonparametric statistical comparisons were made among the median growth rates of all of the treatment groups. A significant reduction in median tumor growth rates was observed in animals treated with 100 and 200 mg/Kg of CLT.

Those skilled in the art will be able to ascertain with no more than routine experimentation numerous equivalents to the specific imidazoles and processes described herein. Such equivalents are considered to be within the scope of the invention and are intended to be embraced by the following claims in which

We claim:

1. A method for treating cancer sensitive to treatment with the compounds set forth herein comprising:

administering to a subject that has a nonsteroid-hormone dependent cancer an effective amount of an imidazole selected from the group consisting of clotrimazole, micronazole and econazole.

2. A method for treating cancer as claimed in claim 1, wherein the imidazole is administered to a subject that has a cancer selected from the group consisting of:

biliary tract cancer; brain cancer; breast cancer; cervical cancer; choriocarcinoma; colon cancer; endometrial cancer; esophageal cancer; gastric cancer; hematological neoplasms; intraepithelial neoplasms; liver cancer; lung cancer; lymphomas; neuroblastomas; oral cancer; ovarian cancer; pancreas cancer; rectal cancer; sarcomas; skin cancer; testicular cancer; thyroid cancer; and renal cancer.

3. A method for treating cancer as claimed in claim 1, wherein the imidazole is administered to a subject that has a cancer selected from the group consisting of:

biliary tract cancer; brain cancer; choriocarcinoma; colon cancer; esophageal cancer; gastric cancer; hematological neoplasms; intraepithelial neoplasms; liver cancer; lung cancer; lymphomas; neuroblastomas; oral cancer; pancreas cancer; rectal cancer; sarcomas; skin cancer; thyroid cancer; and renal cancer.

4. A method for treating cancer as claimed in claim 1 wherein the imidazole is administered to a subject that has

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a cancer selected from the group consisting of lung cancer, melanoma, intraepithelial neoplasm, breast cancer, brain cancer, liver cancer and sarcomas.

5 5. A method for treating cancer as claimed in claim 1 wherein the imidazole is administered to a subject that has a cancer selected from the group consisting of lung cancer and melanoma.

6. A method for treating cancer as claimed in claim 1 wherein the imidazole is administered to a subject that has a cancer that is a lung cancer.

7. A method for treating cancer as claimed in claims 1, 2, 3, 4, 5 or 6 wherein the imidazole is clotrimazole.

8. A method for treating cancer as claimed in claim 4 wherein the imidazole is clotrimazole.

9. A method for treating cancer as claimed in claim 5 15 wherein the imidazole is clotrimazole.

10. A method for treating cancer as claimed in claim 6 wherein the imidazole is clotrimazole.

11. A method for treating cancer as claimed in claim 1 wherein the imidazole is administered to a subject that has a cancer selected from the group consisting of brain cancer, breast cancer, cervical cancer, choriocarcinoma, colon cancer, gastric cancer, hematological neoplasm, intraepithelial neoplasm, liver cancer, lung cancer, lymphoma, sarcoma, skin cancer, thyroid cancer and renal cancer.

12. A method for treating cancer as claimed in claim 11 wherein the imidazole administered to a subject that has a brain cancer.

13. A method for treating cancer as claimed in claim 11 wherein the imidazole is administered to a subject that has a breast cancer.

14. A method for treating cancer as claimed in claim 11 wherein the imidazole is administered to a subject that has a cervical cancer.

15. A method for treating cancer as claimed in claim 11 wherein the imidazole is administered to a subject that has a choriocarcinoma.

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16. A method for treating cancer as claimed in claim 11 wherein the imidazole is administered to a subject that has a colon cancer.

17. A method for treating cancer as claimed in claim 11 wherein the imidazole is administered to a subject that has a gastric cancer.

18. A method for treating cancer as claimed in claim 11 wherein the imidazole is administered to a subject that has a hematological neoplasm.

19. A method for treating cancer as claimed in claim 11 wherein the imidazole is administered to a subject that has a intraepithelial neoplasm.

20. A method for treating cancer as claimed in claim 11 wherein the imidazole is administered to a subject that has a liver cancer.

21. A method for treating cancer as claimed in claim 11 wherein the imidazole is administered to a subject that has a lymphoma.

22. A method for treating cancer as claimed in claim 11 wherein the imidazole is administered to a subject that has a sarcoma.

23. A method for treating cancer as claimed in claim 11 wherein the imidazole is administered to a subject that has a skin cancer.

24. A method for treating cancer as claimed in claim 11 wherein the imidazole is administered to a subject that has a thyroid cancer.

25. A method for treating cancer as claimed in claim 11 wherein the imidazole is administered to a subject that has a renal cancer.

26. A method for treating cancer as claimed in claims 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 wherein the imidazole is clotrimazole.

* * * * *

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

2020
 Bogotá, D.C., Abril 28 de 2006

Doctor
EMILIO FERRERO

ASUNTO	Radicación No.	00 097 424
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	6515
	Folios	0

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

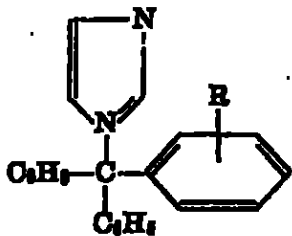
1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 2 - 8 y el capítulo reivindicatorio de los folios 9 - 10 de la solicitud en estudio.

2. Objeto de la invención

El objeto de la presente solicitud de patente de invención consiste en:

Las reivindicaciones 1 - 4 se refieren a composiciones tópicas que tienen como ingrediente activo azoles de fórmula:



como bifonazol, clotrimazol, miconazol, econazol, ketoconazol.

El problema planteado en esta solicitud es la necesidad de compuestos para prevención del cáncer de piel causado por radiaciones.

Para resolver este problema técnico la solicitud en estudio proporciona composiciones tópicas que tienen como ingrediente activo azoles como bifonazol, clotrimazol, miconazol, econazol, ketoconazol.

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El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 61 K 31/4184.

También se reivindica prioridad de la Solicitud de Patente de Alemania 199 63 052.6 de diciembre 24 de 1999, con respecto a la cual la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

3. Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."*

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 24 de diciembre de 1999, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

No.	Documento	Título	Fecha de Publicación
D1	US 3 691 192	Un N-tritil-imidazol	Sept 12, 1972
D2	US 4 833 141	Acidos 4-[4-[[2-(halofenil)-2-[1H-triazol(ó diazol)-1-Il-metil)-1,3-dioxolan-4-Il]metoxi]fenil]-piperazin-1-carbámicos que tienen actividad antimicótica	May 23, 1989
D3	US 5 633 274	Tratamiento de cáncer	May 27, 1997

4. Evaluación de los requisitos de Patentabilidad

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación Industrial".*

En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar el cumplimiento de los requisitos de novedad, nivel inventivo y aplicación industrial, con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

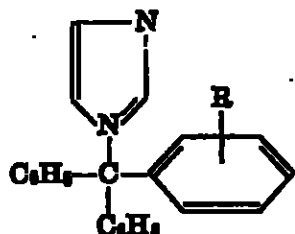
Evaluación de la Novedad

El Art. 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente, o, en su caso, de la prioridad reconocida."*

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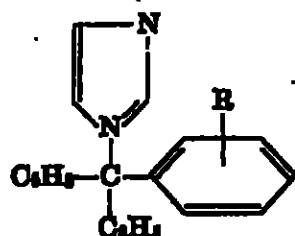
Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el Art 40°.

Las reivindicaciones 1 – 4 se refieren a composiciones tópicas que tienen como ingrediente activo azoles de fórmula:



como bifonazol, clotrimazol, miconazol, econazol, ketoconazol.

D1 enseña (ver folios 62 y 63) azoles de fórmula:



D2 menciona azoles antimicóticos como miconazol y ketoconazol.

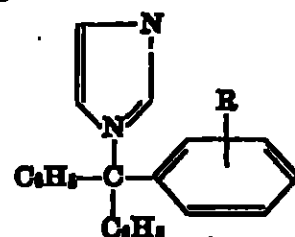
D3 enseña azoles como clotrimazol, miconazol y econazol para tratamiento de cáncer.

Se observa que la estructura de los compuestos azol que caracterizan a las composiciones de las reivindicaciones 1 - 4, como clotrimazol, miconazol, econazol, ketoconazol, ya era conocida en las anterioridades D1, D2 y D3. Por lo cual no pueden considerarse nuevas.

Evaluación del Nivel Inventivo

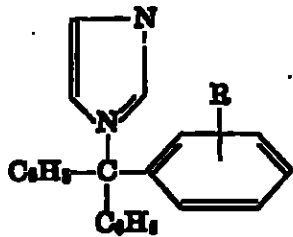
El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.*

Las reivindicaciones 1 – 4 se refieren a composiciones tópicas que tienen como ingrediente activo azoles de fórmula:



como bifonazol, clotrimazol, miconazol, econazol, ketoconazol.

D1 enseña (ver folios 62 y 63) azoles de fórmula:



D2 menciona azoles antimicóticos como miconazol y ketoconazol.

D3 enseña azoles como clotrimazol, miconazol y econazol para tratamiento de cáncer.

Se observa que

- (a) la estructura de los compuestos azol que caracterizan a las composiciones de las reivindicaciones 1 - 4, como clotrimazol, miconazol, econazol, ketoconazol era evidente para una persona conocedora de la materia; considerando los compuestos de las anterioridades D1, D2, D3; y para una persona conocedora de la materia era evidente el elaborar las composiciones de manera similar, teniendo en cuenta estos compuestos;
- (b) las reivindicaciones de esta solicitud no mencionan una característica de la estructura química de los compuestos que les conceda un efecto diferente o especial, ni a las composiciones, que pueda considerarse como un aporte a la técnica, así que son obvias para una persona versada en la materia;
- (c) el problema planteado en esta solicitud que era la necesidad de compuestos para prevención del cáncer de piel causado por radiaciones se resuelve proporcionando composiciones tópicas que tienen como ingrediente activo azoles como bifonazol, clotrimazol, miconazol, econazol, ketoconazol, es decir de manera similar a como se resolvía en las anterioridades;
- (d) el resultado obtenido: composiciones tópicas que tienen como ingrediente activo azoles como bifonazol, clotrimazol, miconazol, econazol, ketoconazol no es inesperado.
- (e) no parece haberse superado un prejuicio técnico anterior, con las composiciones propuestas

Por todo lo anterior se observa que las composiciones reivindicadas son obvias y evidentes para una persona versada en la materia, de manera que no tienen nivel inventivo.

5. Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 3 691 192	1 - 4	Novedad y Nivel Inventivo
D2	US 4 833 141	1 - 4	Novedad y Nivel inventivo
D3	US 5 633 274	1 - 4	Novedad y Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal

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e), del capítulo quinto del título primero de la Circular Unica No. 10 de 2001.



ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista, de fecha
15 JUN. 2006

CONCEPTO TÉCNICO No. 701	EXAMINADOR TÉCNICO Código 202007
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

75

RADICACIÓN: 0-87424

EDICTO No. 17304

**LA SECRETARÍA GENERAL AD-HOC
HACE SABER:**

Que esta Superintendencia profirió Resolución No. 28172 de 28-OCT-2006. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

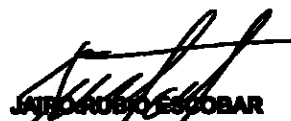
ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "USO DE AZOLES PARA LA PREVENCION DEL CANCER DE PIEL".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Emilio Ferrero, o a quien haga sus veces, en su calidad de apoderado de Bayer Aktiengesellschaft., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los **26 Oct. 2006**

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIRO RUBIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc 09-NOV-2006
Secretaría General Ad-Hoc
EDICTO No. 17304

Este edicto se desfija hoy 23-NOV-2006 a las cinco (5:00 p.m.)