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# TRIANA, URIBE & MICHELSEN

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 06-029537- -00004-0000
Fecha: 2008-02-22 15:51:18 Dep: 2020 NUECREACIONE
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 538 PETICION Folios: 2

MINISTERIO DE COMERCIO INDUSTRIA Y TURISM
SUPERINTENDENCIA DE INDUSTRIA Y COMERCI
DIVISION DE NUEVAS CREACIONES
E. S. D.

REFERENCIA : SOLICITUD DE REGISTRO DE LA PATENTE DE INVENCIÓN **COMPUESTO ARTEMISININA** EXPEDIENTE No. 06029537
CODIGO : 01 – 01 - 09

**LAURA MICHELSEN NIÑO**, mayor y vecina de esta ciudad, identificada como aparece al pie de mi firma, actuando como apoderada de **GUOQIAO LI y JIANPING SONG**, domiciliados en la ciudad de Guangdong, China, por medio de la presente me permito solicitar que se efectúe el examen de patentabilidad de la invención de la referencia, teniendo en cuenta lo siguiente:

1. Que el artículo 44 de la Decisión 486 de la Comunidad Andina establece que dentro del plazo de seis (6) meses contados desde la publicación de la solicitud el solicitante debe pedir que se examine si la invención es patentable.

2. Que la patente de la referencia fue publicada en la Gaceta de Propiedad Industrial No. 580 del veintiocho (28) de septiembre de dos mil siete (2007), y como tal se está dentro del término indicado para solicitar el mencionado examen.

3. Adjunto a la presente anexo el recibo de pago correspondiente a los derechos oficiales por el presente trámite.

De la Señora Jefe,

LAURA MICHELSEN NIÑO
C.C. No. 39.783.287 de Usaquén
T.P.A. No. 45.265 del C.S de la J.

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RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 06-029537- -00004-0000

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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FECHA : FEBRERO 21 DE 2008

***** C O N S I G N A C I O N *****

| DEPOSITANTE | TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PGO | Vr. PAGO |
|---|---|---|---|---|---|---|
| TRIANA URIBE & MICHELSEN | CONSIGNACION | BANCO DE BOGOTA | 062754387 | 598779 | 21/02/2008 | 30,850,100.00 |

***** C O N C E P T O *****

| CANT. | RENTISTICO | CONCEPTO | | TOTAL CONCEPTO |
|---|---|---|---|---|
| 1 | 50005-01-01 SOLICITUDES | 85 | EXAMEN DE PATENTABILIDAD DE INVEN | 420,000.00 |
| | | | TOTAL : $ | 420,000.00 |

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

Industria y Comercio
SUPERINTENDENCIA

**DIVISIÓN DE NUEVAS CREACIONES**

RADICACIÓN EXPEDIENTE No. 06-29537

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **580** DE

FECHA **28 DE SEPTIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR

LA LEY EXPIRA EL **27 DE DICIEMBRE DE 2007**

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 caiga 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___

D1

Med Toxicol Adverse Drug Exp. 1987 Jul-Aug;2(4):242-73.

**Clinical features and management of poisoning due to antimalarial drugs.**

Jaeger A, Sauder P, Kopferschmitt J, Flesch F.

The toxicities of antimalarial drugs vary because of the differences in the chemical structures of these compounds. Quinine, the oldest antimalarial, has been used for 300 years. Of the 200 to 300 compounds synthesised since the first synthetic antimalarial, primaquine in 1926, 15 to 20 are currently used for malaria treatment, most of which are quinoline derivatives. Quinoline derivatives, particularly quinine and chloroquine, are highly toxic in overdose. The toxic effects are related to their quinidine-like actions on the heart and include circulatory arrest, cardiogenic shock, conduction disturbances and ventricular arrhythmias. Additional clinical features are obnubilation, coma, convulsions, respiratory depression. Blindness is a frequent complication in quinine overdose. Hypokalaemia is consistently present, although apparently self-correcting, in severe chloroquine poisoning and is a good index of severity. Recent toxicokinetic studies of quinine and chloroquine showed good correlations between dose ingested, serum concentrations and clinical features, and confirmed the inefficacy of haemodialysis, haemoperfusion and peritoneal dialysis for enhancing drug removal. The other quinoline derivatives appear to be less toxic. Amodiaquine may induce side effects such as gastrointestinal symptoms, agranulocytosis and hepatitis. The main feature of primaquine overdose is methaemoglobinaemia. No cases of mefloquine and piperaquine overdose have been reported. Overdose with quinacrine, an acridine derivative, may result in nausea, vomiting, confusion, convulsion and acute psychosis. The dehydrofolate reductase inhibitors used in malaria treatment are sulfadoxine, dapsone, proguanil (chloroguanide), trimethoprim and pyrimethamine. Most of these drugs are given in combination. Proguanil is one of the safest antimalarials. Convulsion, coma and blindness have been reported in pyrimethamine overdose. Sulfadoxine can induce Lyell and Stevens-Johnson syndromes. The main feature of dapsone poisoning is severe methaemoglobinaemia which is related to dapsone and to its metabolites. Recent toxicokinetic studies confirmed the efficacy of oral activated charcoal, haemodialysis and haemoperfusion in enhancing removal of dapsone and its metabolites. No overdose has been reported with artemesinine, a new antimalarial tested in the People's Republic of China. The general management of antimalarial overdose include gastric lavage and symptomatic treatment.

D2

**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant *(for all designated States except US)*: WASHINGTON UNIVERSITY [US/US]; One Brookings Drive, St. Louis, MO 63130 (US).

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(75) Inventors/Applicants *(for US only)*: PIWNICA-WORMS, David, R. [US/US]; 45 Godwin Lane, St. Louis, MO 63124 (US). SHARMA, Vijay [CA/US]; 9940 Warshire Drive, St. Louis, MO 63132 (US).

(74) Agents: FOX, Samuel, L. et al.; Sterne, Kessler, Goldstein & Fox, P.L.L.C., Suite 600, 1100 New York Avenue, N.W., Washington, DC 20005-3934 (US).

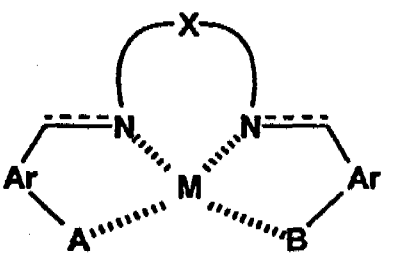
(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*

(54) Title: MULTIDENTATE METAL COMPLEXES AND METHODS OF MAKING AND USING THEREOF

(57) Abstract

The invention relates to multidentate metal complexes having formula (I) wherein M is Fe, In, Ga or Al; the dashed lines represent independently a sigle or a double bond; the hatched lines represent coordination to the metal cation (M); A and B are oxygen, or in the case where Ar is 2-pyridyl or 2-pyrrolyl, a shared pair of electrons on the nitrogen; Ar is optionally substituted phenyl, optionally substituted naphthyl, optionally substituted 2-pyridyl or optionally substituted 2-pyrrolyl, with the proviso that at least one of the substituents comprises a boron atom; X is alternatively (i) $(CHR^2)_p[NR^3(CHR^4)_q]_r$, wherein p and q are independently 1, 2, 3, 4, 5 or 6; r is 0, 1 or 2; and $R^2$, $R^3$ and $R^4$ are independently hydrogen, lower alkyl or phenyl, or two adjacent $R^2$ or $R^4$ groups represent a double bond or a fused benzene ring where p or q, respectively, is greater than 2; with the proviso that where r is 1 or 2, then there are 1 or two additional sites of coordination to the metal; or (ii) optionally substituted phenyl, wherein the phenyl, when substituted, has lower alkyl substituents, optionally with: proviso (A), wherein at least one of the substituents of Ar comprises boron, or with proviso (B), wherein at least one of substituents of Ar comprises a linkage to a pharmaceutically active substituent.




(I)

The metal complexes of the present invention may be co-administered with one or more known antimalarial substances. The known antimalarial substances can be divided into the following 6 main groups on the basis of their chemical compositions:

1) the 9-aminoacridines (e.g., mepacrine),
2) the 4-aminoquinolines (e.g., amodiaquine, chloroquine, hydroxychloroquine),
3) the 8-aminoquinolines (e.g., primaquine, quinocide),
4) the biguanides with an inhibiting effect on dihydrofolic acid reductase (e.g., chloroproguanil, cycloguanil, proguanil),
5) the diaminopyrimidines (e.g., pyrimethamine),
6) the quinine salts.

In addition to these groups, sulphones such as dapsone, sulphonamides, sulphanilamides and antibiotics such as tetracycline may also be used as antimalarial agents.

Depending on their mode of activity the known antimalarial agents can be divided into the following categories:

1. causal prophylactic substances effective against primary tissue stages,
2. active substances directed against relapses or recurrences and effective against latent tissue stages,
3. blood schizonticides,
4. gametocytocides and
5. sporonticides.

The first group includes, for example, proguanil, pyrimethamine and primaquine and derivatives thereof, and also sulphanilamides, sulphonamides and tetracyclines. The second group includes, for example, 8-aminoquinolines, such as primaquine and its analogues and derivatives, floxacrine, cycloguanil, dapsone and quinazolines. Substances active against the blood schizonts include, in particular, 4-aminoacridines such as mepacrine, and the 4-aminoquinolines such

as chloroquine or chloroquinesulphate, quinine, amodiaquine and mepacrine, mefloquine, and related compounds such as halofantrene, pyrimethamine, proguanil, primaquine and the sulphanilamides and sulphonamides, particularly in conjunction with pyrimethamine.

Other substances which may be coadministered are the sesquiterpene lactones based on the compound artemisinine, and the semisynthetic derivatives thereof, such as artesunate, artemether, piperaquine, hydroxypiperaquine, pyronaridine, halofantrene and, generally, the biguanides and quinine salts.

The schizonticides mentioned above are effective against the schizonts of, for example, *P. vivax, P. malariae* or *P. ovale*, but not against the mature gametocytes. The 8-aminoquinolines, such as primaquine and quinocide, are also effective against the gametocytes. Proguanil, primaquine and pyrimethamine are also sporonticidal agents. Other known antimalarial agents are: chloroproguanil, cycloguanil (e.g., as a salt of embonic acid), pamaquine, plasmocide, totaquine, spirogermanium, febrifugine, brusatol, bruceine-A, bruceine-B, bruceine-C, yadanziolide-A, tebuquine, enpirolin, eurycomanone, 3-(4-imidazolyl)-2-(pivaloylamido)-propionylhydrazide, cinchonidine; cucurbitacine, tripynadine, 5-ethylthioribose, arteether (ethylether analogues of artemether), artenilic acid, pyrexol, atalaphillinine, diformyldapsone, bruceantine, nitroquine, octanoylprimaquine, pyrimethamine plus sulfadoxine, hivernine, dabequine, artelinic acid, mefloquinquinate, halfantrin-beta-glycerophosphate, nimbolide, sergeolide (quassinoid of *Picrolemma pseudocoeffea*), simalikalactone-D, fluoroquine, fluorenmethanol, isouramil, cycloleucine, acedapsone (diacetyldapsone), gentiopicrine, amquinate (amquinolate), endochine, pentaquine, isopentaquine, methylchloroquine, amopyroquine, quinine, hydroquinine (dihydroquinine), dimeplasmine, azacrine, diapromine, menoctone, cycloquine (haloquine), lapinone, aristoquine, cloguanamil, clociguanil, brindoxime, cinchonine, tripiperaquine, 3-hydroxy-2-(4-(4-phenyl)-cyclohexyl)-1,4-anthraquinone, aminodiaquine, 4-methyl-5-n-pentoxyprimaquine, 4-methyl-5-n-hexoxyprimaquine, 2-(4-(4-chlorophenyl)-cyclohexyl)-3-hydroxy-1,4-

naphthalenedione, gossypol derivatives, halofantrine (1,3-dichloro-α-(2-(dibutylamino)ethyl)-6-(trifluoromethyl)-9-phentantrene-methanol), cinchona alkaloids (e.g., in the combination quinine, quinidine, cinchonine), N,N'-bis(3-((phenylmethyl)amino)propyl)-1,8-octanediamine, N,N-bis(3-((phenyl-methyl)amino)-propyl)-1,7-diaminoheptane, selenium-analogues of 2-acetyl and 2-propionyl-pyridinethiosemicarbazones, tebuquine, 2,6-bis(1-piperidinylmethyl)-4-((7-(trifluoromethyl)-4-quinolinyl)amino)-phenol, primary phosphoric acid esters of 4'-chloro-5-(1,1-dimethylethyl)-3-(((1,1-dimethylethyl)amino)methyl)-(1,1'-biphenyl-2-ol, N4-(2,6-dimethoxy-4-methyl-5-(3-trifluoromethyl)-phenoxy-8-quinolinyl)-1,4-pentanediamine, N,N-diethyl-N'-(6-methoxy-4-methyl-8-quinolinyl)-1,6-hexanediamine, 5-(N-aryl-tropan-3-yl)- and 5-(piperidin-4-yl)-2,4-diamino-pyrimidine, 4'-amino-4-n-propylamino-2-methyl-diphenylsulphone, 5-ethylthioribose, riboflavin-analogues, 1-(3-(2,4-dichlorophenoxy)-1,6-dihydro-6,6-dimethyl-1,3,5-triazine-2,4-diamine as the monohydrobromide, 1,6-dihydro-6,6-dimethyl-1-(3-(2,4,5-trichlorophenoxy)-propoxy)-1,3,5-triazine-2,4-diamine as the monohydrochloride, trans-2-(4-(1,1-dimethylethyl)-cyclohexyl)-3-hydroxy-1,4-naphthalenedione, enpiroline, mirincamycin, tripynadine, 3-(4-imidazolyl)- 2-(pivaloylamido)propionylhydrazide, 2-acetylpyridine-thiosemicarbazones and the pyrrolidine derivatives thereof.

The present invention also relates to the use of these complexes for their cytotoxic activity on other cell types. Such cell types include cancer cells such as CNS tumors, breast cancer, lung, head and neck, cancer lymphoma, leukemias, ovarian carcinoma, sarcomas, renal cell carcinoma, and prostate cancer.

Thus, the invention is also related to a method of treating cancer comprising contacting said cells with an effective amount of one of the multidentate cationic metal complexes of the present invention. Such contacting will typically be carried out by administration *in vivo* to an animal.

The present invention also relates to the use of these metal complexes as potentiators of photodynamic therapy. Light-absorbing chemicals such as the

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所引用双字母代码和其它缩写符号, 请参考刊登在每期PCT公报期刊起始的"代码及缩写符号简要说明"。

(54) Title: PHARMACEUTICAL COMPOSITION OF DIHYDROARTEMISININ FOR TREATING MALARIA

(54) 发明名称: 用于治疗疟疾的双氢青蒿素药物组合物

(57) Abstract: The present invention provides a composition for treating malaria, comprising dihydroartemisinin, piperaquine and trimethoprim as well as their analogs and salts. Said compositions exhibit therapeutic action rapidly with high efficiency and low toxicity in animal models and clinical tests. The period of treatment when administrating the composition above is much shorter than that when using other antimalarials. The composition according to the invention contains dihydroartemisinin and piperaquine as the essential principles which are demonstrated to be synergetic.

(57) 摘要

本发明提供一种治疗疟疾的双氢青蒿素组合物, 包括双氢青蒿素、哌喹、甲氧苄啶及其类似物及盐。该组合物通过动物试验和临床试用表明具有速效、高效、低毒、短疗程的特点, 其疗效和低毒副作用明显优于目前国内外的同类药。本发明组合物中两个主要成分, 即双氢青蒿素和哌喹相配伍也有较好效果, 为本发明的重要组成部分。

WO 02/26226 A1

US005219865A

# United States Patent [19]

Chatterjee et al.

[11] Patent Number: 5,219,865

[45] Date of Patent: Jun. 15, 1993

[54] **PHARMACEUTICAL COMBINATION FOR THE PROPHYLAXIS AND THERAPY OF MALARIA**

[75] Inventors: **Dipak C. Chatterjee**, Bombay; **Bindumadhavan Venugopalan**, Maharashtra; **Bansi Lal**; **Noel J. de Souza**, both of Bombay, all of India; **Richard H. Rupp**, Königstein/Taunus, Fed. Rep. of Germany

[73] Assignee: **Hoechst Aktiengesellschaft**, Frankfurt am Main, Fed. Rep. of Germany

[21] Appl. No.: **865,624**

[22] Filed: **Apr. 9, 1992**

**Related U.S. Application Data**

[63] Continuation of Ser. No. 565,167, Aug. 10, 1990, abandoned, which is a continuation of Ser. No. 191,172, May 6, 1988, abandoned.

[30] **Foreign Application Priority Data**

May 8, 1987 [DE] Fed. Rep. of Germany ..... 3715378

[51] **Int. Cl.**[5] ..... **A61K 31/44**; A61K 31/47; A61K 31/335

[52] **U.S. Cl.** ..... **514/305**; 514/314; 514/450

[58] **Field of Search** ..... 514/314, 450, 305

[56] **References Cited**

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(List continued on next page.)

*Primary Examiner*—Jerome D. Goldberg

*Attorney, Agent, or Firm*—Farabow, Garrett & Dunner Finnegan, Henderson

[57] **ABSTRACT**

The present invention relates to combinations of the malaria therapeutics artemisinine, dihydroartemisinine, arteether, artemether, artesunate or other artemisinine derivatives with one or more of the antimalarials chloroquine, 10-0-methylfloxacrine, quinine, mefloquine, amodiaquine, pyrimethamine, sulfadoxine and primaquine. Synergistic actions are achieved with them on treatment of mammals, including humans, with subcurative doses of the individual substances.

**2 Claims, No Drawings**

# PHARMACEUTICAL COMBINATION FOR THE PROPHYLAXIS AND THERAPY OF MALARIA

This application is a continuation of application Ser. No. 07/565,167, filed Aug. 10, 1990, now abandoned which is a continuation of application Ser. No. 07/191,172, filed May 6, 1988, now abandoned.

The present invention relates to a combination of the malaria therapeutics artemisinine and its derivatives, for example dihydroartemisinine, arteether, artemether or artesunate, with one or more of the antimalarials chloroquine, 10-0-methylfloxacrine, quinine, mefloquine, amodiaquine, pyrimethamine, sulfadoxine, primaquine and the pharmaceutically utilizable salts thereof, for potentiating the action, and to dosage methods for these combinations of active substances.

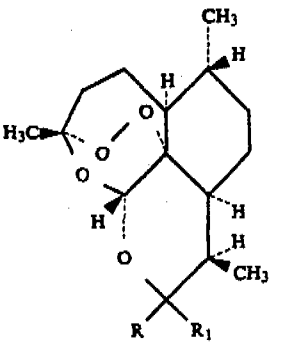
The generic names used here and elsewhere in the text are taken from "Tropical Diseases Research, Seventh Programme Report", chapter 2; Malaria, UNDP-/WORLD BANK/WHO, published by the WHO in 1985; 10-0-methylfloxacrine is a derivative of the antimalarial floxacrine and has been described in German Patent Application P 36 24 778.2.

Malaria which is resistant to medicaments represents a serious problem for clinical care and public health. The malaria parasite Plasmodium falciparum has developed a versatile ability to elude the action of a medicament by either genetic mechanisms or non-genetic (adaptive) methods. It has been demonstrated that the chloroquine resistance of malaria parasites takes the form of a stable genetically determined property (Warhurst, D. C. Pharmaceut. J. Nov. 23 (1985) 689-692). The spread of Plasmodium falciparum resistant to chloroquine and other antimalarials presents the public health programs in tropical and subtropical countries with a difficult task (Suphat et al., Trans. R. Soc. Trop. Med. and Hyg. (1983) 73 (3), 338-340). The use of combinations of various antimalarials in the chemotherapy of malaria is known. Thus, for example, a combination of amodiaquine and tetracycline and a combination of pyrimethamine and sulfadoxine, which is known under the name Fansidar®, has been used in clinical care (Suphat et al. cit.). More recently, clinical studies have been started on another antimalarial combination, Fansimef (mefloquine, pyrimethamine and sulfadoxine) (WHO loc. cit.).

Peters has reported (Peters et al., Ann. Trop. Med. and Parasit. 71 (1977), 407-418) that the development of resistance can be slowed down in an animal study if one antimalarial is administered in combination with certain other antimalarials. Peters (W. Peters, Bull. W. H.O. 51 (1974), 379-383 and W. Peters, Handbook of Experimental Pharmacology 68/11 (1984) Springer Verlag Berlin, Heidelberg, New York, Editors: W. Peters and W. H. G. Richards) has also drawn attention to the use of appropriate medicament combinations for the treatment of malaria in humans, these not only being able to delay the development of resistance but also improving the success of treatment. Thus, for example, it has been demonstrated that a triple combination of mefloquine, sulfadoxine and pyrimethamine delayed the development of resistance of Plasmodium berghei (Merkli et al., Ann. Trop. Med. and Parasit. (1980), 4 (1), 1-9).

Artemisinine and derivatives have likewise already been disclosed as antimalarials. Artemisinine was isolated from Artemisia annual L., subsequently synthesized and used for the treatment of P. falciparum malaria (H. P. Koch, Pharm. Int. (1981), 184-185; L. J. Bruce-Chwatt, British Med. J. 284 (1982), 767-768). It has also proved to be effective against chloroquine-resistant strains of P. falciparum in humans. Dihydroartemisinine, arteether, artemether and artesunate, for example, are semisynthetic derivatives of artemisinine, and the action thereof against malaria has been described in various reports (W. H. O. Report of the Scientific Working Group on the Chemotherapy of Malaria, PDR/Chemal 3rd Review, 85.3, Geneva, June 3-5, 1985, and references contained therein).

Artemisinine and its derivatives are represented by formula I



I

with R and $R_1$ together denoting oxygen (artemisinine), or J R denoting in each case hydrogen, and $R_1$ denoting OH (dihydroartemisinine), —O—$C_1$-$C_6$—alkanoyl, —O—$C_1$-$C_6$—carboxyalkanotyl, —O—cyclo—hexy carbonyl, —O—benzoyl or —O—naphthoyl, as well as the corresponding pharmacologically tolerated salts.

The compound of the formula I with R =H and $R_1$ =—O—$CH_3$ is called artemether, that with R =H and $R_2$ =—O—$C_2H_5$ is called arteether, and that with R =H and $R_1$ =—O—$COCH_2CH_2CO_2Na$ is called artesunate.

It has now been found, surprisingly, that combinations of artemisinine and/or its abovementioned derivatives with the known malaria therapeutics chloroquine, 10-0-methylfloxacrine, quinine, mefloquine, amodiaquine, pyrimethamine, sulfadoxine, primaquine and the pharmaceutically utilizable salts thereof show a synergistic action.

The clinical importance of the present improved compositions for malaria therapy is reflected by relevant animal experiments. The specific examples which follow contain typical test protocols used to examine the ability of the test substance to be an effective antimalarial even for medicament-resistant strains of P. berghei.

The present combination of antimalarials which is described in more detail hereinafter permits the desired malaria treatment, specifically both for prophylaxis and for therapy, and prevents or delays the development of resistance.

Artemisinine or one of its abovementioned derivatives is administered to mammals in general in the range 0.125-10 mg/kg in a single dose each day for 5 days. The other antimalarial which has already been mentioned hereinbefore in this specification (i.e. chloroquine, 10-0methylfloxacrine, quinine, pyrimethamine, mefloquine, amodiaquine, sulfadoxine and primaquine) can be administered separately; in this case, the latter is administered in an amount within the (although usually

lower) dose range and in accordance with the treatment regimens (frequency, dosage form and compositions) as are specified for the use thereof in publications to date, for example in the references cited above or further in the said references.

It is advantageous and more convenient to administer artemisinine or one of its derivatives and further antimalarials of the invention in a single combined composition. This can be a form suitable for parenteral administration, but a form suitable for oral administration is to be preferred. The proportion of each medicament in the proposed combined dosage form corresponds to the proportion of the total daily dose of each medicament when it is administered alone. The combined medicaments can be administered in single or divided doses.

In the preferred oral administration, the amount of artemisinine for an average adult patient will in general be in the range 0.2–2 g in combination with 200–400 mg of chloroquine or with 200–400 mg of 10-0-methylfloxacrine as initial dose; the 2nd dose can be administered 6 hours later in the range 0.2–2 g of artemisinine in combination with 100–200 mg of chloroquine or with 100–200 mg of 10-0-methylfloxacrine. The dose administered at the second intake can be maintained for a further 3 days, with a single dose being administered each day.

Combinations of artemisinine or one of its derivatives with other antimalarials of the second group can be administered in a similar manner. In general, a combination of dihydroartemisinine (range 0.2–1.5 g) with chloroquine (range 200–400 mg) or with 10-0-methylfloxacrine (range 200–400 mg) can be administered to an adult patient, with administration 6 hours later of a second dose of 0.2–1.5 g of dihydroartemisinine in combination with 100–200 mg of chloroquine or with 100–200 mg of 10-0-methylfloxacrine. The amount administered as the 2nd dose can in general be administered as a single dose each day for a further 3 days.

It is also possible to administer to an adult patient a combination of arteether (range 0.2–1.5 g) together with chloroquine or with 10-0-methylfloxacrine (range 200–400 mg). The 2nd dose can be administered 6 hours after the 1st dose and can contain 0.2–1.5 g of arteether plus 100–200 mg of chloroquine or 10-0-methylfloxacrine. The amount administered with the 2nd dose can in general be given as a single dose each day for a further 3 days.

The combined substances are administered, both orally and parenterally, alone or in a further combination with pharmaceutically utilizable vehicles. On oral administration, the suitable pharmaceutical vehicles include inert diluents or extenders used for the preparation of tablets, powders, capsules or the like. These pharmaceutical combinations can, if this is desired, contain additional ingredients such as flavorings, binders, corrigents or the like. For example, tablets which contain various corrigents such as sodium citrate, together with various soluble substances such as starch, alginates and certain complex silicates and binders such as polyvinylpyrrolidone, sucrose, gelatin and gum arabic, are used. In addition, lubricants such as magnesium stearate, sodium lauryl sulfate and talc are often suitable for the preparation of tablets. Solid compositions of a similar nature are also used as fillers in filled soft and hard gelatin capsules. Accordingly, the preferred materials include lactose and polyethylene glycols of high molecular weight.

The present invention is illustrated by the examples which follow. However, it ought to be pointed out that the invention is not confined to the specific details of the examples.

## EXAMPLE 1

Synergistic therapeutic actions of subcurative doses of artemisinine, dihydroartemisinine and arteether in combination with subcurative doses of chloroquine, 10-0-methylfloxacrine, mefloquine or pyrimethamine against chloroquine-sensitive Plasmodium berghei infection in Swiss mice.

## METHODOLOGY OF THE BIOLOGICAL EVALUATION

The assessment of the schizontocidal action in the blood from the "28-day test" described by Raether and Fink (Ann. Trop Med. and Parasit., 73 (1979), 503–526) was used for this.

## MICE

All the experiments were carried out with randomly bred male and female Swiss mice which originated from the rearing unit of Hoechst India Limited in Muland, Bombay. The animals were free of Eperythrozoon coccoides. The animals received dry feed and water ad lib. and were housed at a room temperature of 22–25° C.

## PARASITE

The London School of Hygiene and Tropical Medicine supplied the strain Plasmodium berghei K-173 which is sensitive to medicaments, and P. berghei (NS) which is moderately resistant to chloroquine. The strains elicit, after they have been inoculated intraperitoneally, a lethal infection with $1 \times 10^7$ parasite-infected erythrocytes per mouse.

## ADMINISTRATION OF THE SUBSTANCES

The substances were administered orally or subcutaneously by the methods described by Raether and Fink (loc. cit.). Artemisinine, dihydroartemisinine and arteether were homogenized in doubly refined corn oil and used as suspensions for the subcutaneous inoculation of mice. The medicaments were administered for 5 days. The 1st dose was given within 2 hours after the infection (D+0), followed by D+1, D+2, D+3 and D+4 (intervals of 1 day each).

## OBSERVATION OF THE TREATED MICE

From D+4 to D+28 blood smears were prepared at various intervals. The blood smears were obtained from the distal end of the tail and were stained with Giemsa solution. The mice were free of P. berghei on D+28 and were regarded as completely cured. At least 12 mice were investigated for each dose.

The synergistic therapeutic action of subcurative doses of artemisinine, dihydroartemisinine and arteether, each in combination with subcurative doses of chloroquine, mefloquine, pyrimethamine or 10-0-methylfloxacrine, on mice infected with chloroquine-sensitive P. berghei is shown in Table I for oral, and in Table II for subcutaneous,

TABLE I

| Composition | Oral dose (mg/kg × 5) | Mice per group | % infected animals cured |
|---|---|---|---|
| Chloroquine (curative dose) | 12.5 | 25 | 100 |
| Chloroquine (subcurative dose) | 10 | 27 | 40 |
| 10-O-Methylfloxacrine | 10 | 12 | 100 |

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**
**DIVISIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogada
LAURA MICHELSEN NIÑO
(Apoderado)

| | | |
|---|---|---|
| ASUNTO | Radicación | 06029537 |
| | Trámite | 002 |
| | Evento | 001 |
| | Actuación | 430 |
| | Oficio | 0851 5 |
| | Folios | 015 |

Patente de Invención [X] Patente de Modelo de Utilidad [ ]

Vía Nacional [ ]

Vía PCT (fase nacional) [X] Cap.I [X] Cap. II [ ]

No. Sol. Internacional PCT/CN2004/001064
Fecha de Presentación Internacional 20-09-2004

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

**1. Documentos estudiados:**

1.1. Descripción: (Folios: 26 a 37) como se radicó inicialmente. Modificaciones (Folios: 40 a 43).

1.2. Reivindicaciones: 1 a 2 (Folios: 37 y 38) como se radicó inicialmente. Modificadas 1 a 2 (Folios: 43 y 44).

1.3. Prioridad: 26/09/2003 CN 03146951.5.

**2. Análisis de la Prioridad:**

La prioridad de la presente solicitud no corresponde totalmente al objeto reivindicado, puesto que en la prioridad se reclama en la reivindicación 2 "una combinación que comprende artemisinina de acuerdo con la reivindicación 1, donde la primaquina puede estar formulada en una tableta para ser tomada junto con una tableta de artemisinina + piperaquina", mientras que en la presente solicitud, esta misma reivindicación dice que "la primaquina puede estar formulada en una tableta para ser tomada junto con una tableta de artemisinina + piraquinina".

3. **Objeto de la invención:**

La presente solicitud se titula: "Compuesto artemisinina".

El objeto de la presente solicitud se refiere a medicamentos para el tratamiento de malaria, en particular, a un compuesto que contiene artemisinina con un efecto terapéutico alto y rápido.

De acuerdo con la descripción, entre las drogas contra la malaria de la técnica anterior, algunas emplean derivados de artemisinina (tales como dihidroartemisinina, artesunato, artemeter, ateéter) en conjunto con piperaquina presentando una vida media larga. Los efectos laterales del tracto GI, tales como náuseas y vómito debido a una cantidad considerable de fosfatos que afectan adversamente los efectos terapéuticos, con incidencia del hasta 10% cuando la cantidad total para un curso de administración se divide en 3 dosis, y se reduce a 3-5% cuando se divide en 4 dosis. Adicionalmente, las drogas contra la malaria anteriores presentan las desventajas de un largo periodo de procesamiento, alto costo de producción, vida de estantería corta, altas dosis y similares.

En el capítulo reivindicatorio se reclama lo siguiente:

Reivindicación 1 (folios: 43 y 44): Una combinación que comprende artemisinina, que se puede formular en tabletas o gránulos, supositorios, suspensión en jarabe o polvo seco para uso pediátrico, dicha combinación comprende artemisinina, piperaquina y primaquina en los siguientes rangos de proporciones:
Artemisinina 1 parte
Piperaquina 5 partes
Primaquina 0 - 0,05 partes
Siendo la proporción óptima 1:5:0,04.

Reivindicación 2 (folio: 44): Una combinación que comprende artemisinina de acuerdo con la reivindicación 1, donde la primaquina puede estar formulada en una tableta por separado para tomarse junto con una tableta mixta de artemisinina + piraquina.

El problema planteado en esta solicitud es la necesidad de una combinación para el tratamiento de la malaria que tenga un menor costo de materiales, un tamaño menor, un curso de tratamiento de menor duración y una administración más conveniente, así como la habilidad de matar gametófitos para bloquear la expansión de la malaria.

La solución propuesta por la presente solicitud consiste en una combinación que comprende artemisinina, piperaquina y primaquina.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/336, 31/4706, 31/496; A61P 33/06.

4. **De la solicitud de Patente**

4.1. Descripción *(artículo 28 D. 486)*

De acuerdo con lo revelado en la descripción, el título de la solicitud no es consecuente con lo que se pretende proteger; es decir, el título se relaciona con "compuesto de artemisinina" mientras que en el capítulo reivindicatorio se está reclamando "una combinación de artemisina, piperaquina y primaquina".

4.2. Reivindicaciones *(artículo 30 D 486)*

De acuerdo con lo revelado en el capítulo reivindicatorio, se debe aclarar el término "combinación" puesto que no se comprende si se trata de una composición farmacéutica que contiene artemisinina, piperaquina y primaquina, o se trata de dos o más formulaciones farmacéuticas de artemisinina, piperaquina y primaquina que se combinan para lograr un efecto terapéutico contra la malaria.

En la reivindicación 2, se debe aclarar si se está hablando de una mezcla de artemisinina y primaquina o es como se encuentra escrito: "artemisinina y piraquinina".

**5. Unidad de Invención** *(artículo 25 D 486)*

Según lo anterior la (s) reivindicación (es) 2 (folio: 44), que se refiere(n) a una combinación que comprende artemisinina de acuerdo con la reivindicación 1, donde la primaquina puede estar formulada en una tableta por separado para tomarse junto con una tableta mixta de artemisinina + piraquina, no guarda(n) unidad de invención con la reivindicación 1, que se relacionan con una combinación de artemisinina, piperaquina y primaquina en unas proporciones dadas; en la reivindicación 2 se está hablando de dos formulaciones que se administran combinadas para lograr un efecto, mientras que en la 1 se menciona una única formulación que comprende 3 principios activos.

6. **Excepciones de Patentabilidad** *(artículo 20 D486 literal a)-d))*

De acuerdo con lo anterior, la(s) reivindicación(es): 2 (folio: 44 ), que se refiere(n) a una combinación que comprende artemisinina, no es (son) patentable(s) porque tal como se encuentra redactada esta reivindicación se está reclamando un método de tratamiento que consiste en administrar una tableta de artemisinina junto con una tableta de artemisinina + piraquinina.

7. **Análisis de la(s) Oposición(es):** *(artículo 43 D. 486)*

No se presentaron oposiciones al objeto reivindicado.

8. **Determinación del Estado de la Técnica:**

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 26-09-2003.

Teniendo en cuenta la fecha indicada, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se encontró como anterioridades que pueden afectar la patentabilidad del objeto de la presente solicitud:

| Nº | Documento | Título | Fecha de Publicación |
|---|---|---|---|
| D1 | Artículo 1 | Clinical features and management of poisoning due to antimalarial drugs[1] | Julio-agosto de 1987 |
| D2 | WO 96/40108 | Multidentate metal complexes and methods of making and using thereof | 19 de diciembre de 1996 |
| D3 | WO 02/26226 | Pharmaceutical composition of dihydroartemisinin for treating malaria | 4 de abril de 2002 |
| D4 | US 5219865 | Pharmaceutical combination for the prophylaxis and therapy of malaria | 15 de junio de 1993 |

**9. Análisis de patentabilidad (artículo 14 D486)**

9.1. Nivel inventivo *(artículo18 D486)*

La presente Solicitud de Patente reivindica lo siguiente: Una combinación que comprende artemisinina, que se puede formular en tabletas o gránulos, supositorios, suspensión en jarabe o polvo seco para uso pediátrico, dicha combinación comprende artemisinina, piperaquina y primaquina en los siguientes rangos de proporciones:
Artemisinina 1 parte
Piperaquina 5 partes
Primaquina 0 - 0,05 partes
Siendo la proporción óptima 1:5:0,04.

La anterioridad "Clinical features and management of piosoning due to antimalarial

1 Jaeger A., Sauder P., Kopferschmitt J., Flesch F. "Clinical features and management of poisoning due to antimalarial drugs". Med. Toxicol Adverse Drug Exp. 1987 Jul-Ag:2(4):242-73.

drugs" (artículo 1) (folio: 71) menciona algunos aspectos de toxicicidad de algunos antimaláricos y menciona la existencia de la primaquina desde el año 1926, composiciones de piperaquina y de artemisinina; se dice que la mayoría de estos fármacos se administran en combinación para lograr un mejor efecto antimalárico.

El documento WO 96/40108 (folios: 72 a 75) hace mención de las distintas sustancias antimaláricas que hay y su clasificación; entre las 8-aminoquinolinas se encuentra la primaquina y entre las lactonas sesquiterpénicas se encuentra la artemisinina y sus derivados como la piperaquina, las cuales se pueden coadministrar con otros antimaláricos.

La anterioridad WO 02/26226 (folio: 76) se relaciona con una composición farmacéutica de dihidroartemisinina (un derivado de artemisinina), piperaquina y trimetoprim para el tratamiento de la malaria. Se observa que ya existían combinaciones de antimaláricos, por ejemplo derivados de artemisinina con otro tipo de compuesto para lograr un efecto antimalárico.

La anterioridad US 5219865 (folios: 77 a 79) trata sobre una combinación farmacéutica para la profilaxis y terapia de la malaria; las combinaciones consisten en artemisinina, dihidroartemisinina, arteéter, artemeter, artesunate u otros derivados de artemisinina con uno o más antimaláricos como la primaquina. Con estas combinaciones se logra un efecto sinérgico y se emplean dosis más bajas de los compuestos activos.

Estos documentos encontrados demuestran que ya existían las formulaciones de artemisinina y sus derivados como la piperaquina y formulaciones de primaquina; además, estos documentos revelan que ya se hacían combinaciones de distintos antimaláricos para conseguir un mejor efecto terapéutico, de menor duración y el empleo de bajas dosis de estos fármacos para disminuir los efectos colaterales propios de éstos mismos.

El problema técnico planteado en esta solicitud: a necesidad de una combinación para el tratamiento de la malaria que tenga un menor costo de materiales, un tamaño menor, un curso de tratamiento de menor duración y una administración más conveniente, así como la habilidad de matar gametófitos para bloquear la expansión de la malaria, se había resuelto previamente mediante composiciones de artemisinina, piperaquina y primaquina ya conocidos(as). Por esta razón se considera que las combinaciones de artemisinina, piperaquina y primaquina reivindicadas en la presente solicitud son evidentes para una persona medianamente versada en la materia.

Las reivindicaciones 1 y 2 de esta solicitud no mencionan una característica que conceda un efecto inesperado o especial a las combinaciones, que pueda considerarse como un aporte a la técnica, así que son obvios para una persona versada en la materia.

Además, puesto que D1, D2, D3 y D4 divulgaban previamente composiciones de artemisinina, piperaquina y primaquina y combinaciones de éstos (folios: 71 a 79), una persona conocedora de la materia motivada por tal sugerencia lograría el objeto

de esta solicitud una combinación de artemisinina, piperaquina y primaquina; de manera que para una persona medianamente versada en la materia sería obvio emplear estos documentos. Por lo cual puede no haber Nivel Inventivo.

10. **Conclusión:**

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

| N° | Documento N° | Reivindicaciones afectadas | Requisito que afecta |
|---|---|---|---|
| D1 | Artículo 1 | 1 y 2 | Nivel Inventivo |
| D2 | WO 96/40108 | 1 y 2 | Nivel Inventivo |
| D3 | WO 02/26226 | 1 y 2 | Nivel Inventivo |
| D4 | US 5219865 | 1 y 2 | 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 e), del capítulo quinto del título primero de la Circular Única N° 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 24 JUL. 2009

| | |
|---|---|
| **CONCEPTO TÉCNICO** No. 2411 | **EXAMINADOR TÉCNICO**<br>Código No. 202005 |