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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Doctor

GIANCARLO MARCENARO JIMÉNEZ

Superintendente Delegado Para la Propiedad Industrial

EXPEDIENTE: 03-078.242

**ASUNTO: Solicitud de patente a nombre de
Syngenta Participations AG.**

Estimado Doctor:

En mi calidad de apoderada de la sociedad solicitante de la patente de la referencia manifiesto a usted lo siguiente:

1. Mediante memorial radicado en ese despacho el 23 de noviembre de 2005, el cual no ha sido resuelto aún, solicité que se realizara el examen de patentabilidad.
2. En vista de que han transcurrido **10 meses**, sin que se haya atendido dicha solicitud, ruego a usted se sirva dar las instrucciones del caso para que se proceda de inmediato a resolver este asunto.

Cordialmente,


JIMENA ESCOBAR URIBE
CC 39.779.452 de Usaquén.
T.P. 68228

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 03-78242

**EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE
INVENCION FUE PUBLICADO EN LA GACETA DE PROPIEDAD
INDUSTRIAL No 552 DE FECHA 31 DE MAYO DE 2005 EL TERMINO
HABIL SEÑALADO POR LA LEY EXPIRA EL 29 DE AGOSTO DEL 2005**

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**



US005436355A

United States Patent [19]**Demchak**[11] **Patent Number:** **5,436,355**[45] **Date of Patent:** **Jul. 25, 1995**[54] **PROCESS FOR MAKING
AVERMECTIN/ZEIN COMPOSITIONS**[75] **Inventor:** Richard J. Demchak, Langhorne, Pa.[73] **Assignee:** Merck & Co., Inc., Rahway, N.J.[21] **Appl. No.:** 191,824[22] **Filed:** Feb. 3, 1994[51] **Int. Cl.⁶** C07D 315/00[52] **U.S. Cl.** 549/264[58] **Field of Search** 549/267; 514/450[56] **References Cited****U.S. PATENT DOCUMENTS**

4,199,569	4/1980	Chabala et al.	424/180
4,427,663	1/1984	Mrozik	424/180
4,587,247	5/1986	Linn et al.	514/222
4,717,718	1/1988	Eckenhoff et al.	514/30
4,874,749	10/1989	Mrozik	514/30
4,963,141	10/1990	Eckenhoff	424/473
5,215,753	6/1993	Wright et al.	424/473

OTHER PUBLICATIONS

H. Mrozik, et al., J. Organic Chemistry, 1982, 47, pp. 489-492.

John C. Chabala, et al. J. Med. Chem. 1980, 23, pp. 1134-1136.

Primary Examiner—C. Warren Ivy*Assistant Examiner*—A. A. Owens*Attorney, Agent, or Firm*—Sylvia A. Ayler; Mark R. Daniel

[57]

ABSTRACT

Their is disclosed a novel solvent-depletion process for making an avermectin/zein composition and the composition itself, which has excellent photostability and unexpected bioavailability to foliar-feeding insects. The process consists of depleting a dilute acidic, basic or alcoholic solvent from an emulsified solution of avermectin, zein, and dilute solvent.

13 Claims, No Drawings

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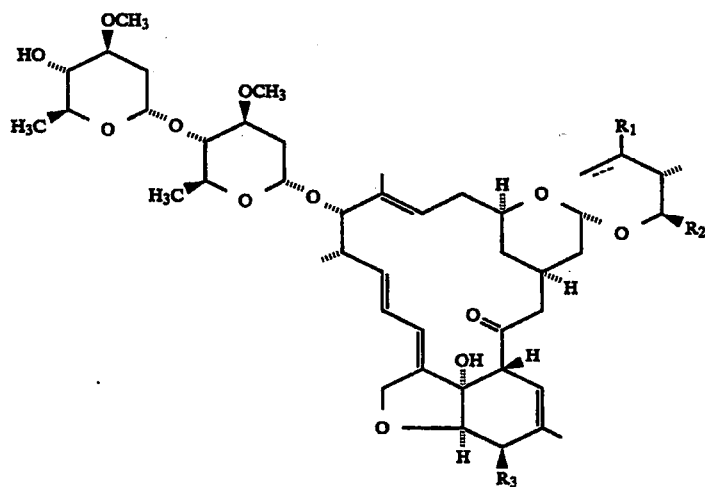
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PROCESS FOR MAKING AVERMECTIN/ZEIN COMPOSITIONS

BACKGROUND OF THE INVENTION

The term avermectin (previously referred to as C-076) is used to describe a series of compounds isolated from the fermentation broth of an avermectin producing strain of *Streptomyces avermitilis* and derivatives thereof. The morphological characteristics of the culture are completely described in U.S. Pat. No. 4,310,519. The natural avermectin compounds are a series of macrolides, each of which is substituted therein at the 13-position with a 4-(α -L-oleandrolyl)- α -L-oleandrose group. Also known are avermectin compounds or pharmaceutically acceptable salts thereof, wherein the 4'' hydroxy group is replaced with an amino or substituted amino (see U.S. Pat. Nos. 4,427,663 and 4,874,749 and pending U.S. patent application Ser. No. 07/862,035). The preparation and properties of synthetic avermectin aglycones in which the disaccharide moiety has been removed leaving a free hydroxyl group at position 13 have been described by Mrozik et al., *J. Org. Chem.* 1982, 47, 489-492 and by Chabala et al., *J. Med. Chem.* 1980, 23 1134-1136. Additionally, U.S. Pat. No. 4,199,569 reveals the 22,23-dihydro avermectin compounds. The avermectin compounds and the instant derivatives thereof have a very high degree of anthelmintic and anti-parasitic activity. The natural compounds have the following general structure:



wherein the broken line at the 22,23-position indicates a single or double bond and;

R₁ is hydroxy and is present only when said broken line indicates a single bond;

R₂ is isopropyl or sec-butyl; and

R₃ is methoxy or hydroxy.

There are eight major natural avermectin compounds, designated A1a, A1b, A2a, A2b, B1a, B1b, B2a and B2b. These designations are based on the structure of the individual compounds as shown in the following table (referring to the foregoing structural formula).

Compound	22,23-bond	R ₁	R ₂	R ₃
A1a	double bond	—	sec-butyl	—OH ₃

-continued

Compound	22,23-bond	R ₁	R ₂	R ₃
A1b	double bond	—	isopropyl	—OH ₃
A2a	single bond	—OH	sec-butyl	—OH ₃
A2b	single bond	—OH	isopropyl	—OH ₃
B1a	double bond	—	sec-butyl	—OH
B1b	double bond	—	isopropyl	—OH
B2a	single bond	—OH	sec-butyl	—OH
B2b	single bond	—OH	isopropyl	—OH

The avermectins are generally isolated as mixtures of the "a" and "b" components (typically $\geq 80\%$ "a" and $\leq 20\%$ "b"). Such compounds differ only in the nature of the R₂ substituent and this minor structural difference has been found to have very little effect on the chemical reactivity or biological activity of the compounds. Thus, although the "a" and "b" components can be separated from each other by chromatography this is not necessary and hence is not normally done. The presence of a mixture of "a" and "b" components may be indicated by dropping the "a" or "b" from the designation of the compound. A mixture of avermectin B1a and avermectin B1b is thus referred to as avermectin B1, or abamectin. Alternatively, a slash(/) is inserted between the compound designations to indicate a mixture such as in "B1a/B1b".

The above structural formula is shown without a definitive stereochemistry at certain positions and with a defined stereochemistry at other positions. However, during the course of the synthetic procedures used to

prepare such compounds, or using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers. In particular, the stereoisomers at the 13- and 23-positions may be oriented either α - or β -representing such groups being below or above the general plane of the molecule, respectively. In each such case, and at other positions in the molecule, both the α - and β -configurations are intended to be included within the ambit of this invention.

A related family of natural products is known as the milbemycins. The milbemycins have the same macrocyclic ring structure as the avermectins but have no substitution at position 13 and have a methyl or ethyl group at position 25 (R₂=methyl or ethyl rather than isopropyl).

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or sec-butyl as in the avermectins). The milbemycins and the fermentation conditions used to prepare them are described in U.S. Pat. No. 3,950,360. Closely related 13-deoxyavermectin aglycones are prepared by chemical modification of the natural avermectins and have been described in U.S. Pat. Nos. 4,171,134 and 4,173,571.

SUMMARY OF THE INVENTION

The instant invention is concerned with a solvent-depletion process for making an avermectin/zein composition and the composition itself, which has excellent photostability and unexpected bioavailability to foliar-feeding insects. A key feature of the process is the depletion of a dilute acidic, basic, or alcoholic solvent (a/b/a solvent) such as acetic acid, propionic acid, lactic acid, ethylene glycol, propylene glycol, diethylene glycol, methyl alcohol, formamide, monoethanolamine, water and the like, most preferably acetic acid, from an emulsified solution of avermectin/zein/a/b/a solvent.

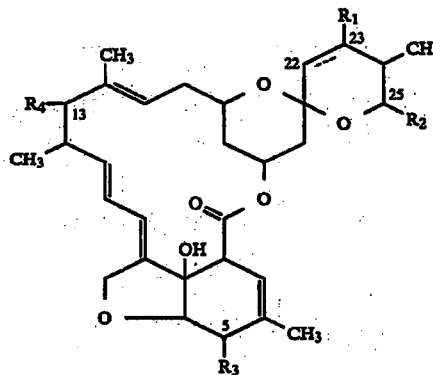
The solution is emulsified in a mineral oil, preferably a mineral oil with a specific gravity of about 0.83 to about 0.88 at 25° C. Under these circumstances, the zein solution forms the dispersed phase while the mineral oil and emulsifier form the continuous phase. The continuous phase is saturated with acetic acid either before or during the emulsification process. The emulsion is pumped and recycled through a suitable semi-permeable membrane that retains the dispersed phase but not the solvent-saturated, continuous phase, which is termed the permeate. Subsequent addition of continuous phase, which has not been solvent saturated, to the emulsion results in depletion of acetic acid from the dispersed phase; ultimately, the dispersed phase consists of avermectin and zein solids suspended in a mineral oil solution. Dodecylamine can optionally be added to the permeate to form the insoluble dodecylamine acetate, in order to recycle the mineral oil.

Thus, it is an object of the present invention to describe such stable avermectin/zein compositions. A further object is to describe the process for the preparation of such compositions. A still further object is to describe the uses of such compositions as anti-parasitic agents and anti-bacterial agents. Still further objects will become apparent from a reading of the following description.

DETAILED DESCRIPTION OF THE INVENTION

The instant composition comprises a solvent-depleted avermectin and zein suspension in mineral oil. The suspension contains a ratio from about 1 to 1 to about 100 to 1 of zein to avermectin, preferably about 3 to 1 to about 25 to 1 of zein to avermectin and from about 60% to about 90% mineral oil.

The avermectin active ingredients and the pharmaceutically acceptable salts thereof such as the benzoate salts in the instant composition have the following structural formula:



where the broken line indicates a single or a double bond at the 22,23-positions;

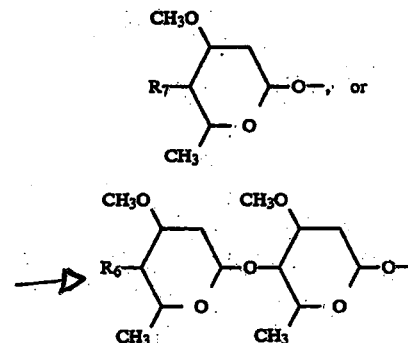
R₁ is hydrogen or hydroxy, and is hydroxy only when the broken line indicates a single bond;

R₂ is alkyl of from 1 to 6 carbon atoms or alkenyl of from 3 to 6 carbon atoms or cycloalkyl of from 3 to 6 carbon atoms;

R₃ is hydroxy, methoxy, or =NOR₅;

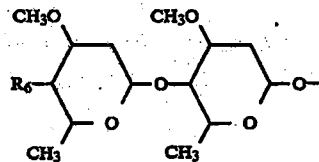
R₅ is hydrogen or C₁-C₃ alkyl; and

R₄ is hydrogen, hydroxy, (C₁-C₃ alkoxy)(-C₀-C₃ alkoxy)methoxy,



where R₆ and R₇ is =O, hydroxy, or R₈R₉-amino, and R₈ and R₉ are independently hydrogen, C₁-C₃ alkyl, C₂-C₃ alkanoyl, substituted benzenesulfonyl wherein the substituent is halogen or C₁-C₃ sulfonyl.

The preferred avermectin active ingredients of the instant composition are wherein R₄ is:



and R₆ is as above and the pharmaceutically acceptable salts thereof.

The instant avermectin/zein compositions are prepared using a solvent-depletion process wherein the a mixture of the avermectin/zein/a/b/a solvent is emulsified and then dialyzed to yield the instant stable bioavailable compositions.

PREPARATION OF STARTING MATERIALS

The starting avermectin materials for this invention are disclosed in Albers-Schonberg et al., *L. Am. Chem. Soc.* 1981, 103, 4216-4221 and references cited therein (naturally occurring avermectins), Chabala et al., *J. Med. Chem.* 1980, 23, 1134-1136 (22,23-dihydro avermectin B1 (ivermectin), 22,23-dihydro avermectin B1-aglycone, U.S. Pat. No. 4,587,247 and U.S. Pat. Nos. 4,427,663 and 4,874,749. Zein is a commercially available protein isolated from corn (See Merck Index 10 ed. page 9918 (1983). The solvents employed are commercially available solvents such as acetic acid, propionic acid, lactic acid, ethylene glycol, propylene glycol, diethylene glycol, methyl alcohol, formamide, monoethanolamine, water and the like.

The active compounds of this invention are potent anti-parasitic agents against external parasitic infestations and are prepared as avermectin/zein compositions with enhanced environmental stability and unexpected bioavailability to foliar-feeding insects.

The avermectin/zein compositions are prepared by dissolving the avermectin compound, from about 1% to about 5%, and the zein from about 5% to about 20% in from about 75% to about 94% of the solvent at ambient temperatures to give a first solution. A small amount of Rhodamine B dye, less than 0.1%, can be added to the first solution to aid in viewing the subsequent emulsion.

A USP Grade mineral oil with a specific gravity of about 0.83 to about 0.88 is used to dissolve from about 5% to about 20% of emulsifier, which is either food-grade lecithin or lecithin fractions to give a second solution. The lecithin fraction/mineral oil solution can be prepared by procedures known to those skilled in the art. For example, 150 grams of food-grade lecithin (>95% acetone insolubles) is added to about 600 mL hexanes, and the components are stirred until most of the lecithin dissolves. If necessary, the solution is allowed to stand to form a sediment and a clear supernatant. Into a 2000 mL flask is added 300 mL of the supernatant and 300 mL ethanol, and the flask is stirred at 40° C. for 1 to 4 hours and then stored at room temperature for 12 to 24 hours. A 300 mL aliquot of the resulting supernatant is removed and discarded, and the solids are redissolved in 600 mL hexanes. The hexane/ethanol fractionation is repeated with the other 300 mL of supernatant, so as to give another hexane solution. The composite solution is evaporated to dryness and the material is stored under vacuum at room temperature. The net weight of the dry material being 110.5 grams, the solid is dissolved in 994.5 grams mineral oil to give 1105 grams of a 10% fractionated lecithin/mineral oil solution.

The first and second solutions are then emulsified with a common homogenizer. Under these circumstances, the zein solution forms the dispersed phase while the mineral oil and emulsifier form the continuous phase. The continuous phase can be diluted with solvent before or during emulsification.

The emulsion is then diffused (dialyzed) through a suitable semi-permeable membrane against mineral oil, which may or may not contain dodecylamine. Alternatively, the emulsion may be pumped through a cross-flow filtration module. The module must allow for sufficient permeate flow for enough time so the depletion process can occur under controlled conditions. A suitable semi-permeable membrane is one with a nominal pore size of 0.2 microns. The semipermeable membrane

retains the dispersed phase and releases the solvent saturated continuous phase as permeate. Additional continuous phase which is not saturated with dilute solvent is then added, resulting in the diffusing solvent such as acetic acid, being removed in the permeate with the process continuing until the solvent is depleted from the dispersed phase of the emulsion. The result is a suspension of avermectin and zein solids in a mineral oil solution. The process can be monitored by analyzing the permeate, e.g., by a titration of acetic acid.

The suspension can be analyzed by standard analytical techniques known to those skilled in the art, such as HPLC. The continuous phase may contain dissolved avermectin, so the final composition of the dispersed phase may differ from the initial composition. In addition, the dispersed phase may contain both avermectin solid and zein solid, as well as a matrix of avermectin and zein. The analyses are conducted so as to add any dispersed avermectin to that dissolved in the mineral oil. Therefore, the ratio of zein to avermectin in the remaining dispersed phase solids is a measure of the quality of the solvent-depletion process and ranges from about 1 to 1 to about 100 to 1 of zein to avermectin.

The photostability of the avermectin/zein systems are also determined using standard procedures known to those skilled in the art. For example, aliquots of the suspension, in conjunction with an avermectin standard, can be stored under conditions with no light and those which are solar simulated and then evaluated for avermectin content.

The instant compositions are unexpectedly potent antiparasitic agents against ectoparasites, particularly arthropods. Ectoparasites are those parasites which live on the outer surface of the host but still draw nutrients from the host.

Infections by ectoparasitic arthropods such as ticks, mites, lice, stable flies, homilies, blowflies, fleas, and the like are a serious problem. Infection by these parasites results in loss of blood, skin lesions, and can interfere with normal eating habits thus causing weight loss. These infections can also result in transmission of serious diseases such as encephalitis, anaplasmosis, swine pox, and the like which can be fatal.

Animals may be infected by several species of parasite at the same time since infection by one parasite may weaken the animal and make it more susceptible to infection by a second species of parasite. Thus, a stable compound with a broad spectrum of activity and excellent bioavailability is particularly advantageous in the treatment of these diseases. The compounds of this invention have unexpectedly high activity against these parasites, and in addition are also active against *Dirofilaria* in dogs, *Nematospides* and *Syphacia* in rodents, biting insects, and migrating dipterous larvae such as *Hypoderma sp.* in cattle, and *Gastrophilus* in horses.

The instant compositions are also useful against ectoparasites which cause parasitic diseases in humans. Ectoparasites which parasitize man include arthropods such as ticks, fleas, mites, lice, and the like and, as with domestic animals, infections by these parasites can result in transmission of serious and even fatal diseases. The instant compositions are active against these ectoparasites and in addition are also active against biting insects and other dipterous pests which annoy humans.

The instant compositions are also useful against common household pests such as *Blatella sp.* (cockroach), *Tineola sp.* (clothes moth), *Attageus sp.* (carpet beetle),

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Musca domestica (housefly) and against *Solenopsis In-victa* (imported fire ant).

The compositions are furthermore useful against agricultural pests such as aphids (*Acyrtosiphon sp.*), locusts, and boll weevils as well as against insect pests which attack stored grains such as *Tribolium sp.* and against immature stages of insects living on plant tissue. The compounds are also useful as a nematocide for the control of soil nematodes and plant parasites such as *Meloidogyne spp.* and lepidopteran pests, which may be agriculturally important.

For use as an antiparasitic agent in animals the instant compounds may be administered topically as a liquid drench or as a shampoo. Topical application of the instant composition is possible through the use of a liquid drench or a shampoo containing the instant compounds as an aqueous suspension. These formulations generally contain a suspending agent such as bentonite and normally will also contain an additional emulsifying agent. Formulations containing from about 0.005 to about 10% by weight of the active ingredient are acceptable. Preferred formulations are those containing from about 0.01 to about 5% by weight of the instant compounds.

The instant compositions are primarily useful as antiparasitic agents for the treatment and/or prevention of ectoparasites such as ticks, mites, lice, fleas and the like. They are also effective in the treatment of parasitic infections of humans. In treating such infections the compounds of these invention may be used individually or in combination with each other or with other unrelated antiparasitic agents. The dosage of the instant compounds required for best results depends on several factors such as the species and size of the animal, the type and severity of the infections, the method of administration and the compound used. Topical administration of the instant compositions containing active compounds at a dose level of from about 0.0005 to about 10 mg per kg of animal body weight, either in a single dose or in several doses spaced a few days apart, generally gives good results. A single dose of one of the instant composition normally gives excellent control however repeat doses may be given to combat re-infection or for parasite species which are unusually persistent. The techniques for administering these compounds to animals are known to those skilled in the veterinary field.

The instant compositions may also be used to combat agricultural pests which attack crops either in the field or in storage. The compositions are applied for such uses as sprays, emulsions and the like either to the growing plants or the harvested crops. The techniques for applying these compounds in this manner are known to those skilled in the agricultural arts.

The following examples is provided in order that this invention might be more fully understood; it is not to be construed as limitative of the invention. The avermectin derivative prepared in the following example is characterized using techniques such as High Performance Liquid Chromatography (HPLC), and the like.

EXAMPLE 1

Lecithin/Mineral Oil/abamectin (as hexanol solvate) Solution

A 10% solution of fractionated lecithin/mineral oil (1105 g) is combined with 100 mg of abamectin and the system stirred at room temperature. The system is then filtered to give a clear lecithin/mineral oil/abamectin

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solution, which is used as the continuous phase for emulsification of the system.

EXAMPLE 2

Abamectin/Zein Microcapsules

In a 1-liter vessel fitted with a stirrer, homogenizer, and addition funnel which has been cooled to approximately 20° C., is added 500 mL of the 10% lecithin/mineral oil/abamectin solution (continuous phase). Acetic acid (25mL) was then added with stirring. The abamectin/zein solution (dispersed phase) was prepared from 1.00 grams abamectin (as hexanol solvate), glacial acetic acid (46.25 grams), zein (5.00 grams), and Rhodamine B (6 rag); the solution was stirred at room temperature for 24 hours. The dispersed phase solution was then added and the solution emulsified until the temperature rose to 25° C. The addition funnel was then filled with 250 mL of lecithin/mineral oil/abamectin solution which was added over a period of 90 minutes with stirring (this step was once repeated). The resulting emulsion was then pumped and recycled through a 0.2 micron pore size semi-permeable membrane, adding approximately 200 mL of additional lecithin/mineral oil solution during the process. The resulting suspension consisting of avermectin and zein solids in a mineral oil solution (microcapsules ratio of 43 to 1 zein to avermectin) was then isolated from the vessel by vacuum filtration.

EXAMPLE 3

The avermectin microcapsules were compared to abamectin —0.15 EC (control) for photostability under a solar simulator. The zein suspension and EC, each of which contained about 0.01 mG of avermectin B 1a were deposited in petri dishes with an area of about 175 cm², using cyclohexane as a diluent for both compositions. Four dishes, two for each composition, were placed under a solar simulator, while one dish for each composition was placed in a dark drawer. The dishes were analyzed for avermectin B1a at various times using reversed —phase HPLC and the results showed that avermectin B1a degraded more slowly when combined with zein by the above noted process. The recoveries are shown below:

Conditions Time (Exposure)	Recovery (%)	
	Abamectin-0.15 EC	Abamectin/zein
3 days (dark)	42	85
3 days (light)	1.5	40
4 days (light)	0.6	38

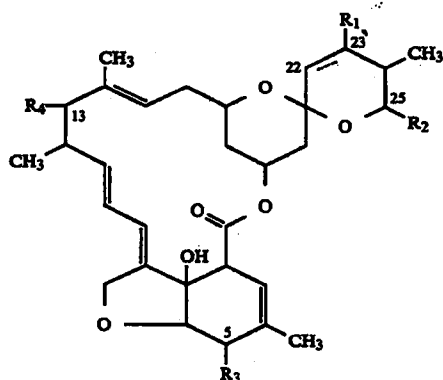
What is claimed is:

1. A solvent-depleted avermectin/zein composition useful for treating plants or animals infected with parasites which comprises avermectin or a pharmaceutically acceptable salt thereof and zein in suspension with a ratio from about 1 to 1 to about 100 to 1 of zein to avermectin and an inert ingredient.

2. The composition of claim 1, wherein the avermectin compound has the structural formula:

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where the broken line indicates a single or a double bond at the 22,23-positions;

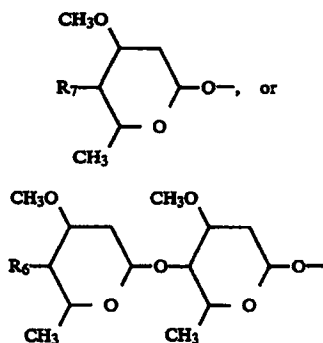
R₁ is hydrogen or hydroxy, and is hydroxy only when the broken line indicates a single bond;

R₂ is alkyl of from 1 to 6 carbon atoms or alkenyl of from 3 to 6 carbon atoms or cycloalkyl of from 3 to 6 carbon atoms;

R₃ is hydroxy, methoxy, or =NOR₅;

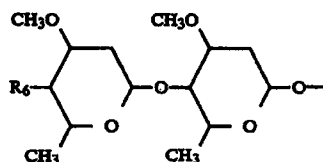
R₅ is hydrogen or C₁-C₃ alkyl; and

R₄ is hydrogen, hydroxy, (C₁-C₃ alkoxy)(-C₀-C₃ alkoxy)methoxy,



where R₆ and R₇ is =O, hydroxy, or R₈R₉-amino, and R₈ and R₉ are independently hydrogen, C₁-C₃ alkyl, C₂-C₃ alkanoyl, substituted benzenesulfonyl wherein the substituent is halogen or C₁-C₃ sulfonyl.

3. The composition of claim 2 wherein R₄ is:



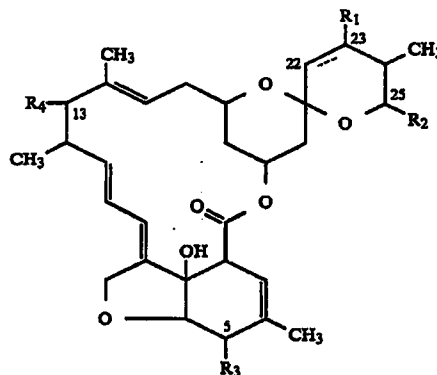
R₆ is as above, the avermectin and zein is suspended in mineral oil and the zein to avermectin ratio is from about 3 to 1 to about 25 to 1.

4. A solvent-depletion process for making avermectin/zein compositions which comprises contacting avermectin or a pharmaceutically acceptable salt thereof and zein with a dilute acidic, basic, or alcoholic solvent, emulsifying the avermectin/zein/solvent solution in a mineral oil with an emulsifier to form a dispersed phase consisting of the avermectin/zein and solvent and a

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continuous phase consisting of the mineral oil and emulsifier, saturating the continuous phase with the solvent before or during emulsification, pumping and recycling the resulting emulsion through a semi-permeable membrane which retains the dispersed phase and releases the solvent-saturated continuous phase as permeate and adding additional continuous phase which is not saturated with solvent, resulting in depletion of the solvent from the dispersed phase, thereby making the avermectin/zein composition suspended in the mineral oil solution.

5. The process of claim 4, wherein the avermectin compound has the structural formula:



where the broken line indicates a single or a double bond at the 22,23-positions;

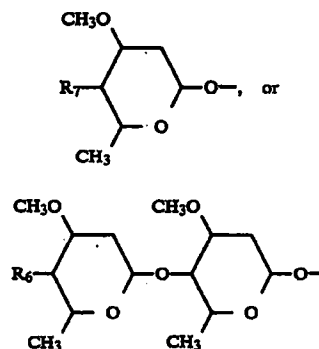
R₁ is hydrogen or hydroxy, and is hydroxy only when the broken line indicates a single bond;

R₂ is alkyl of from 1 to 6 carbon atoms or alkenyl of from 3 to 6 carbon atoms or cycloalkyl of from 3 to 6 carbon atoms;

R₃ is hydroxy, methoxy, or =NOR₅;

R₅ is hydrogen or C₁-C₃ alkyl; and

R₄ is hydrogen, hydroxy, (C₁-C₃ alkoxy)(-C₀-C₃ alkoxy)methoxy,



where R₆ and R₇ is =O, hydroxy, or R₈R₉-amino, and R₈ and R₉ are independently hydrogen, C₁-C₃ alkyl, C₂-C₃ alkanoyl, substituted benzenesulfonyl wherein the substituent is halogen or C₁-C₃ sulfonyl.

6. The process of claim 4 wherein R₄ is:

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EUROPEAN PATENT APPLICATION

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51 Int. Cl.⁵: C07H 17/08, C07D 493/22,
A61K 31/70, A01N 43/90

22 Date of filing: 20.12.89

30 Priority: 23.12.88 US 289118

43 Date of publication of application:
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CH DE FR GB IT LI NL

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54 Avermectin derivatives.

57 Synthetically modified avermectin derivatives are disclosed containing novel alkyl, and alkenyl substituents at position 25 and having additional substituents at positions 4'- and 4"- of the oleandrose structural part. The compounds are prepared from the known C-25 substituted avermectin derivatives by the appropriate chemical reactions at the 4'-, and 4"-positions. The new compounds are potent antiparasitic agents, in particular, the compounds are anthelmintic, insecticidal and acaricidal agents.

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corresponding keto compound. During the procedure the presence of a hydroxy group at the 5-position will require that such hydroxy group be protected in order that it too is not oxidized. The 23-hydroxy group is less reactive and the 7-hydroxy group is very unreactive and inert and they need not be protected. The procedure used to prepare the protected intermediates are described above. The oxidation reaction is carried out in an inert solvent such as methylene chloride using oxalyl chloride or trifluoroacetic anhydride and dimethylsulfoxide as the oxidizing agent. Additionally, N-chlorosuccinimide and dimethylsulfide may be employed. The reaction proceeds by dissolving the oxalyl chloride or trifluoroacetic anhydride and dimethylsulfoxide (or other oxidizing reagents) in methylene chloride with cooling from -50° to -80° C and adding dropwise a methylene chloride solution of the avermectin compound to be oxidized. The addition is carried out over a period of from 15 minutes to 1 hour and then triethylamine is added dropwise over a period of from 1 to 15 minutes. The reaction mixture is then allowed to warm to room temperature over a period of from 1/2 to 1 hour. The 4' or 4''-keto compound is isolated using techniques known to those skilled in the art.

In the next step, the 4' or 4''-keto compound is aminated to prepare the unsubstituted amino compound. The reaction is carried out in an inert solvent such as methanol at from -25° to +10° C using ammonium salts and sodium cyanoborohydride as the aminating and reducing reagents. The reaction is complete in from 15 minutes to 2 hours and the product 4''-deoxy-4'-amino compound (or the corresponding 4' compound) is isolated using techniques known to those skilled in the art. Suitable ammonium salts are the acetate, propionate, benzoate and the like. The acetate is preferred.

As a variation to the foregoing amination reaction, alkyl ammonium salts could be used in place of the ammonium salts to prepare the mono alkyl substituted compounds directly. The same reagents, salts and reaction conditions as described above can be used for such a reaction.

The substitution reaction of the newly formed amino group wherein the substituent is an acyl function is carried out using an acylating reagent in the presence of a base in an inert solvent. The preferred acylating reagents are loweralkanoyl anhydrides, loweralkanoyl halides, substituted benzene sulfonyl chlorides, lower alkyl sulfonyl chlorides, and the like. The reaction is carried out in an inert solvent such as methylene chloride in the presence of a non-reactive base such as pyridine or triethylamine in order to neutralize the acid produced during the course of the reaction. The reaction temperature is from -10° to 25° C and the reaction is complete in from 5 minutes to 1 hour. The product is isolated using known techniques.

The reaction for the preparation of the 4''-deoxy-4'-dimethylamino compounds (or the corresponding 4'-compound) is carried out using the alkylating reaction conditions of formaldehyde and a reducing agent such as sodium borohydride, in methanol. The reaction is carried out in aqueous medium using excess aqueous formaldehyde along with the presence of a small amount of acid such as acetic acid to facilitate the reaction. The reaction is carried out at from -10° to +10° C with the solution of the 4''-deoxy-4'-amino-avermectin compound in methanol added dropwise over a period of from 30 to 60 minutes to the alkylating reagent mixture and the product is isolated using known techniques. See U.S. Patent 4,427,663.

The reactions which produce the various 4' or 4'' derivatives, such as the keto, amino and substituted amino by the selective oxidation of the 4'' or 4' hydroxy to 4'' or 4' keto which is then reacted with an amino to prepare the amino compounds, are also detailed in U.S. 4,427,663 to Mrozik.

The 4'' or 4' imino compounds are also prepared from the 4'' or 4' keto compounds by reaction with the appropriately substituted semicarbazide, acyl or sulfonyl hydrazine and the like. The reaction is carried out in a non-reactive solvent at from 20 to 80° C in from 30 minutes to 48 hours. The products are isolated using techniques known to those skilled in the art.

Further reactions of avermectins are described in the chemical literature and are reviewed by Fisher M.H., Mrozik H. (1984) The avermectin family of macrolide-like antibiotics. In Omura S. (ed) Macrolide Antibiotics, Academic Press, New York, pp 553-606, and by Davies H.G., Green A.S. (1986) Avermectins and Milbemycins. Nat. Prod. Rep. 3:87-121.

The instant compounds with an acyl function at the 5, 4' or 4'' positions are prepared by acylating the various hydroxy groups at such positions of the avermectin compounds. In particular the 5-hydroxy, 4'-hydroxy or the 4''-hydroxy, groups can be reacted with acylating agents to prepare the appropriate acylated derivative. Such compounds are prepared using the appropriate reactive intermediates such as the acid chloride, anhydride, carbamoylchloride and the like. The reaction conditions for such reactions are generally well known to those skilled in the art and are further disclosed in U.S. Patent 4,201,861 to Mrozik et. al.

The conversion of the 22,23-double bond into the reduced 22,23-single bond compound by the selective oxidation with Wilkinson's homogeneous catalyst, triphenylphosphine rhodium chloride is described in U.S. 4,199,569 to Chabala et. al.

The novel compounds of this invention have significant parasitocidal activity as anthelmintics, ectoparasiticides, insecticides and acaricides, in human and animal health and in agriculture.

The disease or group of diseases described generally as helminthiasis is due to infection of an animal host with parasitic worms known as helminths. Helminthiasis is a prevalent and serious economic problem in domesticated animals such as swine, sheep, horses, cattle, goats, dogs, cats and poultry. Among the helminths, the group of worms described as nematodes causes widespread and often times serious infection in various species of animals. The most common genera of nematodes infecting the animals referred to above are *Haemonchus*, *Trichostrongylus*, *Ostertagia*, *Nematodirus*, *Cooperia*, *Ascaris*, *Bunostomum*, *Oesophagostomum*, *Chabertia*, *Trichuris*, *Strongylus*, *Trichonema*, *Dictyocaulus*, *Capillaria*, *Heterakis*, *Toxocara*, *Ascaridia*, *Oxyuris*, *Ancylostoma*, *Uncinaria*, *Toxascaris* and *Parascaris*. Certain of these, such as *Nematodirus*, *Cooperia*, and *Oesophagostomum* attack primarily the intestinal tract while others, such as *Haemonchus* and *Ostertagia*, are more prevalent in the stomach while still others such as *Dictyocaulus* are found in the lungs. Still other parasites may be located in other tissues and organs of the body such as the heart and blood vessels, subcutaneous and lymphatic tissue and the like. The parasitic infections known as helminthiasis lead to anemia, malnutrition, weakness, weight loss, severe damage to the walls of the intestinal tract and other tissues and organs and, if left untreated, may result in death of the infected host. The hydrogenated avermectin compounds of this invention have unexpectedly high activity against these parasites, and in addition are also active against *Dirofilaria* in dogs, *Nematospirides*, *Syphacia*, *Aspiculuris* in rodents, arthropod ectoparasites of animals and birds such as ticks, mites, lice, fleas, blowfly, in sheep *Lucilia* sp., biting insects and such migrating dipterous larvae as *Hypoderma* sp. cattle, *Gastrophilus* in horses, and *Cuterebra* sp. in rodents.

The instant compounds are also useful against parasites which infect humans. The most common genera of parasites of the gastro-intestinal tract of man are *Ancylostoma*, *Necator*, *Ascaris*, *Strongyloides*, *Trichinella*, *Capillaria*, *Trichuris*, and *Enterobius*. Other medically important genera of parasites which are found in the blood or other tissues and organs outside the gastrointestinal tract are the filarial worms such as *Wuchereria*, *Brugia*, *Onchocerca* and *Loa*, *Dracunculus* and extra intestinal stages of the intestinal worms *Strongyloides* and *Trichinella*. The compounds are also of value against arthropods parasitizing man, biting insects and other dipterous pests causing annoyance to man.

The compounds are also active against household pests such as the cockroach, *Blattella* sp., clothes moth, *Tineola* sp., carpet beetle, *Attagenus* sp., and the housefly *Musca domestica*.

The compounds are also useful against insect pests of stored grains such as *Tribolium* sp., *Tenebrio* sp. and of agricultural plants such as spider mites, (*Tetranychus* sp.), aphids, (*Acyrtosiphon* sp.); against migratory orthopterans such as locusts and immature stages of insects living on plant tissue. The compounds are useful as a nematocide for the control of soil nematodes and plant parasites such as *Meloidogyne* spp. which may be of importance in agriculture.

These compounds may be administered orally in a unit dosage form such as a capsule, bolus or tablet, or as a liquid drench where used as an anthelmintic in mammals. The drench is normally a solution, suspension or dispersion of the active ingredient usually in water together with a suspending agent such as bentonite and a wetting agent or like excipient. Gradually, the drenches also contain an antifoaming agent. Drench formulations generally contain from about 0.001 to 0.5% by weight of the active compound. Preferred drench formulations may contain from 0.01 to 0.1% by weight. The capsules and boluses comprise the active ingredient admixed with a carrier vehicle such as starch, talc, magnesium stearate, or di-calcium phosphate.

Where it is desired to administer the avermectin derivatives in a dry, solid unit dosage form, capsules, boluses or tablets containing the desired amount of active compound usually are employed. These dosage forms are prepared by intimately and uniformly mixing the active ingredient with suitable finely divided diluents, fillers, disintegrating agents, and/or binders such as starch, lactose, talc, magnesium stearate, vegetable gums and the like. Such unit dosage formulations may be varied widely with respect to their total weight and content of the antiparasitic agent depending upon factors such as the type of host animal to be treated, the severity and type of infection and the weight of the host.

When the active compound is to be administered via an animal feedstuff, it is intimately dispersed in the feed or used as a top dressing or in the form of pellets which may then be added to the finished feed or optionally fed separately. Alternatively, the antiparasitic compounds of our invention may be administered to animals parenterally, for example, by intraruminal, intramuscular, intratracheal, or subcutaneous injection in which event the active ingredient is dissolved or dispersed in a liquid carrier vehicle. For parenteral administration, the active material is suitably admixed with an acceptable vehicle, preferably of the vegetable oil variety such as peanut oil, cotton seed oil and the like. Other parenteral vehicles such as organic preparation using solketal, glycerol formal, and aqueous parenteral formulations are also used. The active monosaccharide or aglycone avermectin compound or compounds are dissolved or suspended in the parenteral formulation for administration; such formulations generally contain from 0.005 to 5% by weight of

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the active compound.

Although the antiparasitic agents of this invention find their primary use in the treatment and/or prevention of helminthiasis, they are also useful in the prevention and treatment of diseases caused by other parasites, for example, arthropod parasites such as ticks, lice, fleas, mites and other biting insects in domesticated animals and poultry. They are also effective in treatment of parasitic diseases that occur in other animals including humans. The optimum amount to be employed for best results will, of course, depend upon the particular compound employed, the species of animal to be treated and the type and severity of parasitic infection or infestation. Generally good results are obtained with our novel compounds by the oral administration of from about 0.001 to 10 mg per kg of animal body weight, such total dose being given at one time or in divided doses over a relatively short period of time such as 1-5 days. With the preferred compounds of the invention, excellent control of such parasites is obtained in animals by administering from about 0.025 to 0.5 mg per kg of body weight in a single dose. Repeat treatments are given as required to combat re-infections and are dependent upon the species of parasite and the husbandry techniques being employed. The techniques for administering these materials to animals are known to those skilled in the veterinary field.

When the compounds described herein are administered as a component of the feed of the animals, or dissolved or suspended in the drinking water, compositions are provided in which the active compound or compounds are intimately dispersed in an inert carrier or diluent. By inert carrier is meant one that will not react with the antiparasitic agent and one that may be administered safely to animals. Preferably, a carrier for feed administration is one that is, or may be, an ingredient of the animal ration.

Suitable compositions include feed premixes or supplements in which the active ingredient is present in relatively large amounts and which are suitable for direct feeding to the animal or for addition to the feed either directly or after an intermediate dilution or blending step. Typical carriers or diluents suitable for such compositions include, for example, distillers' dried grains, corn meal, citrus meal, fermentation residues, ground oyster shells, wheat shorts, molasses solubles, corn cob meal, edible bean mill feed, soya grits, crushed limestone and the like. The active avermectin compounds are intimately dispersed throughout the carrier by methods such as grinding, stirring, milling or tumbling. Compositions containing from about 0.005 to 2.0% weight of the active compound are particularly suitable as feed premixes. Feed supplements, which are fed directly to the animal, contain from about 0.0002 to 0.3% by weight of the active compounds.

Such supplements are added to the animal feed in an amount to give the finished feed the concentration of active compound desired for the treatment and control of parasitic diseases. Although the desired concentration of active compound will vary depending upon the factors previously mentioned as well as upon the particular avermectin derivative employed, the compounds of this invention are usually fed at concentrations of between 0.00001 to 0.00% in the feed in order to achieve the desired antiparasitic result.

In using the compounds of this invention, the individual avermectin components may be prepared and used in that form. Alternatively, mixtures of two or more of the individual avermectin components may be used, or other active compounds not related to the compounds of this invention.

The compounds of this invention are also useful in combatting agricultural pests that inflict damage upon crops while they are growing or while in storage. The compounds are applied using known techniques as sprays, dusts, emulsions and the like, to the growing or stored crops to effect protection from such agricultural pests.

The following examples are provided in order that this invention might be more fully understood; they are not to be construed as limitative of the invention.

The avermectin derivatives prepared in the following examples are generally isolated as amorphous solids and not as crystalline solids. They are thus characterized analytically using techniques such as mass spectrometry, nuclear magnetic resonance, and the like. Being amorphous, the compounds are not characterized by sharp melting points, however, the chromatographic and analytical methods employed indicate that the compounds are pure.

EXAMPLE 1

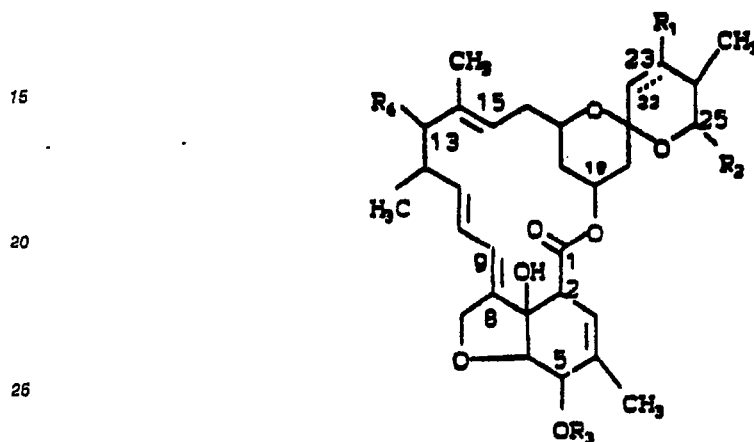
25-Cyclopentyl-25-de-(1-methylpropyl)-4"-oxoavermectin A2a

To a solution containing 0.0195 ml of oxalyl chloride in 1.2 ml of dry CH_2Cl_2 stirred at -78°C is added

A solution of 150 mg of 5-O-tert-butylidimethylsilyl-4"-deoxy-4"-methoxycarbonylamino-25-de-(1-methylpropyl)-25-(1-methylpentyl)avermectin B2a in 2.0 ml of methanol is reacted with a solution of 70 mg of p-toluenesulfonic acid monohydrate in 5.0 ml of methanol at room temperature for 30 minutes as described in example 7 to give 4"-deoxy-4"-methoxycarbonylamino-25-de-(1-methylpropyl)-25-(1-methylpentyl)-
 5 avermectin B2a, which is characterized by its mass and NMR spectra.

Claims

10 1. A compound having the formula:



30 wherein the broken line at the 22,23-position represents a single bond and wherein R₁ is hydrogen or hydroxy, or the broken line represents a double bond and R₁ is absent;

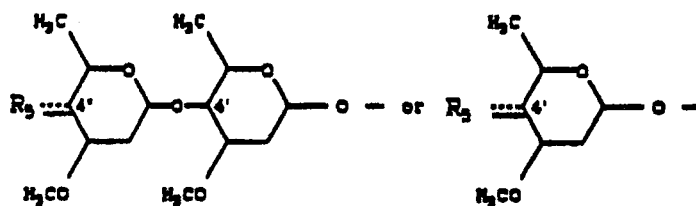
R₂ is an alpha-branched C₃-C₈ alkyl, alkenyl, alkoxyalkyl or alkylthioalkyl group; a C₅-C₈ cycloalkyl substituted C₁-C₄ group; a C₃-C₈ cycloalkyl or C₅-C₈ cycloalkenyl group, either of which may optionally be substituted by methylene or one or more C₁-C₄ alkyl groups or halo atoms; or a 3 to 6 membered oxygen or sulfur containing heterocyclic ring which may be saturated, or fully or partly unsaturated and which may
 35 optionally be substituted by one or more C₁-C₄ alkyl groups or halo atoms, provided R₂ is not 2-propyl, 2-butyl, 2-penten-2-yl, 2-penten-2-yl or 4-methyl-2-penten-2-yl;

R₃ is hydrogen, loweralkyl, or loweralkanoyl;

R₄ is

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50 where the broken line at the 4' and 4" positions indicates a double bond and R₅ is ketone, oxime, hydrazone, loweralkanoylhydrazone, semicarbazone, N-loweralkyl semicarbazone or N,N-diloweralkyl semicarbazone; or the broken line at the 4' and 4" positions indicates a single bond and R₅ is amino, loweralkylamino, diloweralkylamino, lower alkanoylamino, loweralkoxycarbonylamino, carbamoyloxy, N-loweralkylcarbamoyloxy, N,N-diloweralkylcarbamoyloxy, loweralkoxy, loweralkanoyloxy, or loweralkoxycar-
 55 bonyloxy.

2. A compound of Claim 1 wherein the broken line at the 22,23-position represents a single bond and wherein R₁ is hydrogen or hydroxy, or the broken line represents a double bond and R₁ is absent; R₂ is an alpha branched C₃-C₈ alkyl or alkenyl group; a C₅-C₈ cycloalkyl substituted C₁-C₄ alkyl group; a

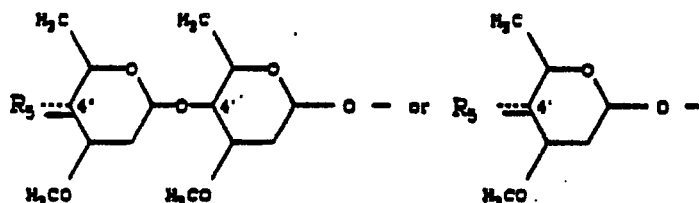
C₃-C₈ cycloalkyl or C₅-C₈ cycloalkenyl group, either of which may optionally be substituted by methylene or one or more C₁-C₄ alkyl groups or halo atoms;

R₃ is hydrogen;

R₄ is

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where the broken line at the 4' and 4'' positions indicates that R₃ is connected by a double bond and R₃ is ketone, loweralkanoylhydrazone, semicarbazone, N-loweralkylsemicarbazone or N,N-dloweralkylsemicarbazone, or the broken line at the 4' and 4'' positions indicates that R₃ is connected by a single bond and R₃ is amino, loweralkylamino, diloweralkylamino, lower alkanoylamino, loweralkyloxycarbonylamino, carbamoyloxy, N-loweralkylcarbamoyloxy, or N,N-dloweralkylcarbamoyloxy.

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3. A compound of Claim 1 wherein the broken line at the 22,23-position represents a single bond and wherein R₁ is hydrogen or hydroxy, or the broken line represents a double bond and R₁ is absent;

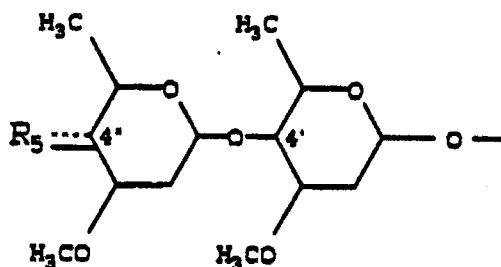
R₂ is 2-pentyl, 2-hexyl cyclobutyl, cyclopentyl, cyclohexyl, 3-thiophenyl, 1-methylthioethyl;

R₃ is hydrogen;

R₄ is

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where the broken line at the 4' position indicates that R₃ is connected by double bond and R₃ is ketone, loweralkanoylhydrazone, semicarbazone, N-loweralkylsemicarbazone or N,N-dloweralkylsemicarbazone, or the broken line at the 4'' position indicates that R₃ is connected by a single bond and R₃ is amino, loweralkylamino, diloweralkylamino, lower alkanoylamino, loweralkyloxycarbonylamino.

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4. 25-Cyclobutyl-25-de-(1-methylpropyl)-4''-deoxy-4'-epi-methylaminoavermectin 8Ia.

5. 25-cyclobutyl-25-de-(1-methylpropyl)-4''-deoxy-22,23-dihydro-4'-methylaminoavermectin 8Ia.

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6. A process for the preparation of the compounds of Claim 1 with an acyl function at the 5, 4' or 4'' positions which comprises acylating the starting material with a hydroxy group at the 5, 4' or 4'' positions.

7. A process for the preparation of the compounds of Claim 1 wherein the 22,23-position is a single bond and R₁ is hydrogen which comprises selectively reducing the 22,23-double bond of the corresponding starting material with Wilkinsons homogenous catalyst, triphenylphosphine rhodium chloride.

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8. A process for the preparation of the compound of Claim 1 wherein R₃ is a ketone or an amino function which comprises selectively oxidizing the 4' or 4'' hydroxy group to a ketone followed by amination of the ketone function.

9. The use of a compound as claimed in Claim 1 for the preparation of a medicament useful for the treatment of parasitic infections.

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10. A composition for the treatment of parasitic infections in animals which comprises an inert carrier and a compound of Claim 1.

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

202085

Bogotá, D.C., 23 de Noviembre de 2007

Abogado

JIMENA ESCOBAR URIBE

ASUNTO

Radicación	03078242
Trámite	002
Evento	001
Actuación	430
Oficio	15946
Folios	23

Patente de Invención

☒

Patente de Modelo de Utilidad

☐

Vía Nacional

☐

Vía PCT (fase nacional)

☒

Cap. I

☐

Cap. II

☒

No. Sol. Internacional: WO 02/24646

Fecha de Presentación Internacional: 26 de Febrero de 2002

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. Capitulo descriptivo: folios 51 al 149 tal y como fueron presentados.

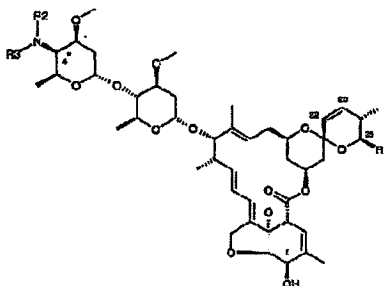
1.2. Capitulo reivindicatorio: folios 150 al 154 tal y como fueron presentados.

1.3. Prioridad: folio 1 CH 374/01 Febrero 27 de 2001.

2. Objeto de la invención

Título de la solicitud: Avermectinas sustituidas en la posición 4 que tienen propiedades pesticidas. Folio 1.

Objeto de la invención: El objeto de la presente solicitud de patente de invención se refiere a un compuesto de formula (I), un proceso para su preparación y el uso de estos compuestos y el de sus tautómeros; pesticidas cuyo compuesto activo se selecciona entre estos compuestos y sus tautómeros; y un proceso para la preparación de estos compuestos y composiciones y uso de estos.



(I)

Reivindicación 1

Un compuesto de la formula (I)

Reivindicación 2

Un pesticida que contiene por lo menos un pesticida de la formula (I)

Reivindicación 3, 7 y 8

Un método para el control de plagas

Reivindicación 4

Un proceso para la preparación de una composición

Reivindicación 5

El uso de un compuesto de la fórmula (I)

Reivindicación 6

El uso de una composición

La literatura propone ciertos compuestos macrólidos para el control de plagas, sin embargo las propiedades biológicas de estos compuestos conocidos no son enteramente satisfactorias. Por lo tanto el problema técnico planteado en la solicitud radica en la necesidad de proporcionar otros compuestos que tengan propiedades pesticidas. Para solucionar este problema técnico la solicitud plantea compuestos de la fórmula (I) derivados de avermectina.

El objeto de la solicitud definido anteriormente se clasificó en la IPC C07H 19/00, A01N 43/22.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

La reivindicación 1 presenta **ampliamente** un compuesto de fórmula (I). Se utilizan términos y expresiones tales como: "o, alquilo, alcoxialquilo, alquenilo, alquinilo, alquilenilo, alquenileno, cicloalquilo, halógeno, haloalquilo, insustituido ó sustituido, arilo, heterocíclico, arioloxi, heterociclioxi, ariltio, heterocicliitio, opcionalmente, o si fuera apropiado un isómero E/Z, mezcla de isómeros E/Z y/o tautómeros del mismo, (entre otros)" que son ambiguos e imprecisos, no definen la materia ni el alcance de la invención y le restan concisión a la reivindicación. Estos términos solamente enuncian superficialmente diferentes funciones químicas que no aportan ninguna caracterización específica a la molécula inicialmente presentada.

La amplia gamma de sustituyentes y la ambigüedad para definirlos conlleva a una gran variedad de estructuras. Y en consecuencia el compuesto de la fórmula (I) no se encuentra definido. Se le recomienda al solicitante que limite y precise cual es la estructura que corresponde al compuesto de la formula (I).

Asimismo sírvase aclarar porque se presenta (folio 153) "...con la condición que R₁ no es sec-butilo ó isopropilo sí R₂ es H y R₃ es..." pues no se encuentra sustento en la descripción para presentar dicha condición y por lo tanto se considera que es una restricción arbitraria no sustentada y que no caracteriza al compuesto de formula (I).

Las reivindicaciones 2 y 4 presentan las expresiones "y/o" y "por lo menos" que son ambiguas y no definen el alcance ni el objeto de la invención.

La reivindicaciones 7 y 8 hacen referencia a un “material de propagación” sin embargo no es claro a que se hace referencia con dicha expresión y su relación con el método de la reivindicación 3. Se le recuerda al solicitante que las reivindicaciones deben ser clara por si mismas.

La reivindicación 8 por su parte no aporta ningún tipo de característica al método de la reivindicación 7, ni hay una relación clara entre los métodos. Por lo tanto las reivindicaciones 3, 7 y 8 no son CLARAS.

En conclusión, estas reivindicaciones no cumplen con el requisito de concisión, claridad y sustento en la descripción de acuerdo al art. 30 de la Decisión 486 o art.22 Tratado PCT.

4. Reivindicaciones relativas a un uso o a un uso distinto (artículos 14 y 21 D 486)

La reivindicaciones 5 y 6 hacen referencia al uso de un compuesto de fórmula (I) y al uso de una composición, respectivamente. Lo cual, de acuerdo, con el artículo 14 no es patentable pues no corresponde a una invención de producto ni de procedimiento.

5. Determinación del Estado de la Técnica

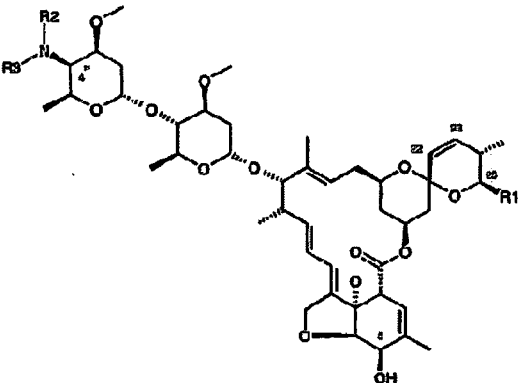
Considerando que la fecha de la prioridad de la solicitud internacional PCT es 27 de febrero de 2001, se realizó la búsqueda en el estado de la técnica y se encontraron los documentos relacionados a continuación, que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
D1	US5436355	Process for making avermectina/zein compositions	1995-07-25
D2	EP0375393	Avermectin derivates	1990-06-27

6. Análisis de patentabilidad (artículo 14 D486)

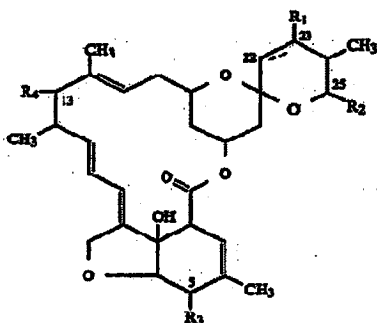
6.1. Novedad (artículo 16 D486)

La presente Solicitud de Patente No. 02078242 en su reivindicación 1, presenta un compuesto de fórmula (I).



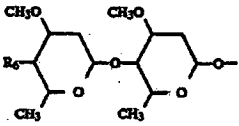
(I)

La anterioridad D1 presenta una composición en la que el compuesto de Avermectina tiene la siguiente fórmula estructural:

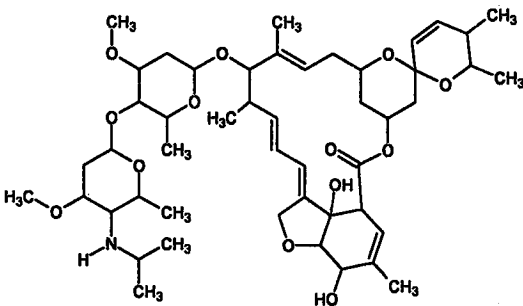


(II)

Por lo tanto cuando se comparan las posibles sustituciones para el compuesto de fórmula (I) con las posibles sustituciones presentadas en la anterioridad, se obtienen estructuras iguales y por lo tanto el documento D1 afecta la novedad de la reivindicación 1. Por ejemplo:

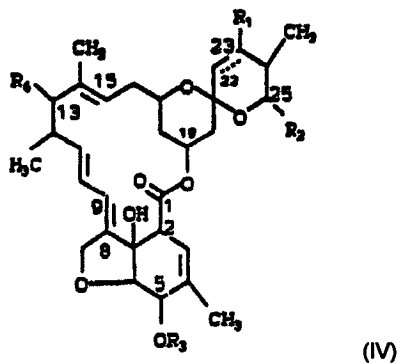
Cuando en la anterioridad D1:	Y cuando en la presente solicitud de patente:
R₁ es H R₃ es OH Entre C₂₂ y C₂₃ hay un enlace doble R₂ es un grupo alquilo de 1 a 6 átomos de carbono o alquenilo de 3 a 6 átomos de carbono o cicloalquilo de 3 a 6 átomos de carbono; R₄ es  R₆ es R₈R₉ amino, y R₈ y R₉ pueden ser independientemente H ó alquilo C₁₋₃.	R₁ es alquilo C₁₋₁₂, cicloalquilo C₃₋₈ ó alquenilo C₂₋₁₂ R₂ es H ó alquilo C₁₋₁₂ R₃ es alquilo C₂₋₁₂

Se obtiene la misma estructura ilustrada en la figura (III) donde, según la solicitud R₁ es metilo, R₂ es H y R₃ es isopropilo. Pero también R₂ y R₃ podrían ser a la vez metilo y aún así la anterioridad D1 sigue afectando la novedad. Por lo tanto la reivindicación 1 no es nueva a partir de D1.



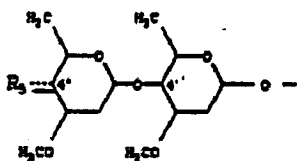
(III)

El mismo análisis se puede realizar con el documento D2 donde se presentan derivados de avermectina de fórmula (IV)



Y cuando:

- la línea punteada representa un doble enlace entre C₂₂ y C₂₃ y el radical R₁ esta ausente.
- R₂ representa alquilo C₃₋₈, alquenilo C₃₋₈ ó cicloalquilo C₅₋₈.
- R₃ es H
- R₄ es



Y R₅ puede estar unido por un enlace sencillo y representa un alquilamino ó dialquilamino de bajo peso molecular.

Se obtiene la misma estructura presentada en la reivindicación 1 de la presente solicitud. En consecuencia la reivindicación no es nueva porque el documento D2 ya había divulgado derivados de avermectina con la misma estructura.

De otro lado, la reivindicación 2 presenta un pesticida que contiene por lo menos un compuesto de fórmula (I) como se describe en la reivindicación 1 como compuesto activo y por lo menos un auxiliar.

El documento D1 presenta composiciones con avermectina como compuesto activo y su aplicación como agentes antiparasitarios y antibacterianos (columna 3). Dichas composiciones son útiles contra insectos ectoparasitarios en animales, humanos y además contra plagas agrícolas (columnas 7 y 8).

Estas composiciones divulgadas en D1 tienen como compuesto activo una avermectina y otros componentes tales como solventes y emulsificantes que son considerados auxiliares comunes en la técnica (ejemplos).

Por lo tanto la reivindicación 2 no es nueva puesto que al comparar los elementos característicos del pesticida con los elementos característicos de la composición del documento D1 se concluye que ya se había formulado una avermectina con otros auxiliares comunes en la técnica.

Asimismo el método presentado en la reivindicación 3 es igual al método divulgado en D1 (columnas 7 y 8) donde se menciona que las composiciones pueden ser aplicadas directamente a las plagas ó sobre el lugar afectado, ya sea animales ó en aplicación agrícola. Nótese que estos métodos son comunes y rutinarios para los expertos en la materia. En consecuencia la reivindicación 3 no es nueva puesto que pal etapa de **aplicación** es la misma en ambos casos.

Por último el proceso presentado en la reivindicación 4 también carece de novedad porque el documento D1 ya había divulgado (ejemplos) un proceso para la preparación de composiciones caracterizado por la **mezcla** de Avermectinas con auxiliares de formulación. Por lo tanto la reivindicación 4 no es nueva y las dependientes de ella tampoco lo son (porque no aportan ninguna otra característica que las pudieran hacer nuevas). Además el proceso de mezcla es un proceso universalmente conocido y no tiene altura inventiva.

De la misma forma la anterioridad D2 afecta la novedad de las reivindicaciones 2 a 4, puesto que este documento ya había divulgado que las Avermectinas tienen una actividad pesticida, parasitaria e insecticida, y pueden ser formuladas en suspensión ó dispersión. Por medio de la **mezcla** de dichos compuestos activos con auxiliares de formulación comunes en la técnica y su posterior **aplicación** sobre la plaga ó el lugar afectado. (Pagina 6 renglones 57-58, pagina 7 renglones 35-37, 43-46, 53-55, página 8 renglones 39-43).

6.2. Nivel inventivo (artículo 18 D486)

Si bien es cierto que algunas de las estructuras resultantes de la reivindicación 1 carecen de novedad a partir de D1 y D2. También se pueden obtener estructuras nuevas debido a la amplitud y variedad de los sustituyentes presentados en la reivindicación 1. Sin embargo, la estructura principal ya ha sido descrita y su actividad pesticida también ha sido divulgada en los documentos D1 y D2. Por lo tanto las posibles nuevas estructuras surgen tan solo como alternativas y resultan ser obvias para una persona medianamente versada en la materia. Por lo tanto ese resto de sustituciones novedosas y posibles nuevas estructuras se derivan de manera obvia del arte previo y carecen de nivel inventivo.

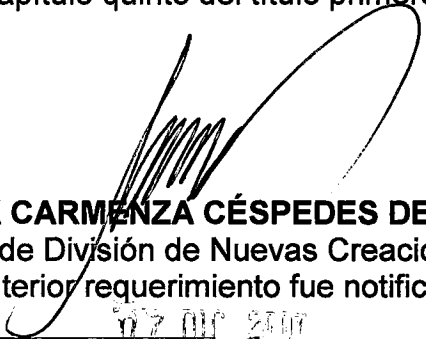
7. **Conclusión**

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

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	US5436355	1-8	Novedad
		1	Nivel Inventivo
D2	EP0375393	1-8	Novedad
		1	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 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 Nº 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL

Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha

07/01/2007

CONCEPTO TÉCNICO No. 2354	EXAMINADOR TÉCNICO Código No.202085
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