



No. 05-059203- -00005-0000

Fecha: 2007-10-05 14:40:04 Dep. 2020 NULCREACION
Eve: 379 HASLNACIONALI
Folios: 13

FORMULARIO ÚNICO DE CORRECCIONES Y MODIFICACIONES

①

SOLICITUD DE:



Corrección de Error Material



Modificación a una solicitud

②

SOLICITANTE

Nombre: MERIAL LIMITED

Dirección: 3239 Satellite Blvd
Duluth
Georgia 30096-4640
Estados Unidos de América

Domicilio: Georgia 30096-4640
Estados Unidos de América

Lugar de Constitución: Estados Unidos
de América

Teléfono:

Fax:

E-mail:

IDENTIFICACIÓN

C.C.



NIT



C.E.



Otro



Cual

Número

③

REPRESENTANTE
O APODERADO

Nombre: MARGARITA CASTELLANOS A.

Dirección: Calle 94 A No. 7 A-09

Teléfono: 610 7420 Fax: 610 0706

E-mail: mail@alvarocastellanos.com

IDENTIFICACIÓN

C.C.



NIT



C.E.



Otro



Cual

Número 39'779.654

TPA

70.819

④

Número de Expediente:

05.059.203

⑤

Descripción de la corrección o modificación solicitada:

Solicito a su despacho tener en cuenta el traspaso de la sociedad SYNGENTA PARTICIPATIONS AG a la sociedad MERIAL LIMITED. Para tal efecto, adjunto el documento de cesión correspondiente así como el documento de Poder otorgado por la sociedad MERIAL LIMITED. En consecuencia, el trámite de la presente solicitud de patente se debe continuar a nombre de la sociedad MERIAL LIMITED.

⑥

Comprobante de pago No.

07-77,932

Fecha

26 de septiembre de 2007

⑦

Anexos:



Comprobante de pago de la tasa.



Poderes si fuere el caso, junto con la sustitución de los mismos a mi favor.



Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas



Nuevo capítulo reivindicatorio

⑧

NOMBRE MARGARITA CASTELLANOS A.

FIRMA



CC 39'779.654 Usaquén - TPA 70.819 CSJ

206

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-059203- -00005-0000

Fecha: 2007-10-05 14:40:04 Dep. 2020 NUECREACION:
Tram. PALENTIA: Ever 379 FASENACIONAL:
Act. 329 C. 000-000-000-000 Folios: 13

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 77,932
FECHA : SEPTIEMBRE 26 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO POPULAR	050-00110-6	63492135	26/09/2007	2,380,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
12		MARCAS Y LEMAS COMERCIALES	79,000.00
TOTAL :			\$ 79,000.00

SON: NOVENTA Y NUEVE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

2007
207

70203/CO
P A T E N T S

CESION

El (los) suscrito (s)

SYNGENTA PARTICIPATIONS AG

en consideración al pago de la suma de
(.....US. \$ 1.00.....), que he(mos)
recibido, por el presente documento cedo
(cedemos) a
MERIAL LIMITED

una compañía constituida de conformidad con las
leyes de Delaware

con oficinas en
3239 Satellite Blvd, Duluth, 30096-4640 Georgia,
Estados Unidos de América.

todos los derechos y títulos sobre la invención
denominada
AVERMECTINA B1 Y DERIVADOS DE
MONOSACARIDOS DE AVERMECTINA B1 QUE
TIENEN UN SUSTITUYENTE ALCOXIMETILO
EN LA POSICION 4' O 4"

Numero de expediente 05.059.203

EL CESIONARIO firma también el presente y
declara que acepta dicha cesión

Dado y firmado hoy

en

Christopher John ANDREWS

Steven Paul WARD

CEDENTE

CESIONARIO

ASSIGNMENT

The undersigned Steven Paul WARD and
Christopher John ANDREWS of

SYNGENTA PARTICIPATIONS AG

in consideration of the sum of
(.....US \$ 1.00.....), the receipt of which
is hereby acknowledged, by these presents do sell,
assign and transfer unto
MERIAL LIMITED

a corporation organized under the laws of
Delaware

having a place of business at
3239 Satellite Blvd, Duluth, 30096-4640 Georgia,
United States of America.

all rights and title to the invention related to

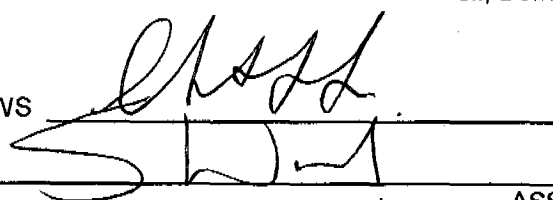
AVERMECTIN B1 AND AVERMECTIN B1
MONOSACCHARIDE DERIVATIVES HAVING AN
ALKOXYMETHYL SUBSTITUENT IN THE 4" O 4'
POSITION

File Number 05.059.203

THE ASSIGNEE signs these presents and declares
that accepts the aforesaid assignment

Given an signed this 25 May 2007

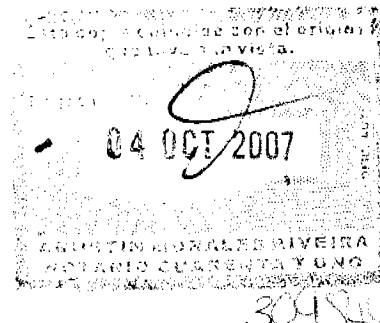
in Bracknell, Berkshire



ASSIGNOR

ASSIGNEE

CASTELLANOS & CO
ABOGADOS COLOMBIA
Calle 94A No. 7A-09- P.O. Box 6349 - Bogotá, Colombia
Tele.: (571) 610 74 20 / - Fax (571) 610 07 06 - e-mail info@castellanosyco.com



208

70203/CO
P A T E N T S

CERTIFICADO NOTARIAL (Cedente)

Yo, Notario Público, CERTIFICO que el 25
DE MAYO
de 2007

Compareció (eron) ante mi

CHRISTOPHER JOHN ANDREWS
STEVEN PAUL WARD

a quien(es) conozco y de quien (es) me consta
que tiene (n) capacidad legal y reconoció(eron)
como suya (s) la (s) firma (s) que aparece (n)
en el documento anterior, cuyo contenido
ratificó(aron)

Doy fé,

Firmado en

NOTARIO PUBLICO

NOTARIAL CERTIFICATE INVENTOR (Assignor)

I, a Notary Public, CERTIFY that on

25th MAY 2007

before me personally appeared

to me known and known to me to be of legal
capacity and acknowledge his (their) signature (s)
appearing on the foregoing instrument and ratified
the same.

I attest,

Signed in

BRACKNELL, BERKSHIRE, UNITED KINGDOM (REINO UNIDO).
25 DE MAYO DE 2007

NOTARIO PUBLICO

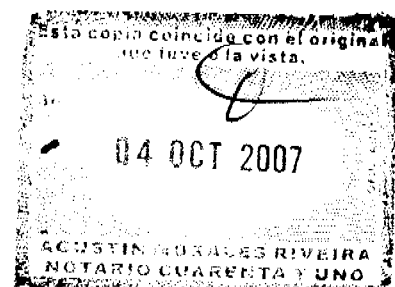
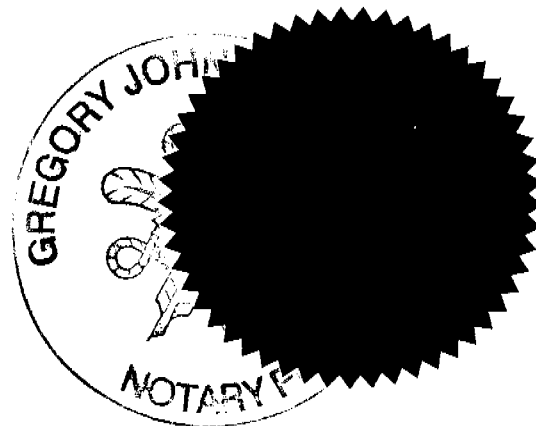

GREGORY JOHN TAYLOR
NOTARY PUBLIC
37 MEADWAY
ASHFORD, MIDDLESEX TW15 2TJ
UNITED KINGDOM

25 DE MAYO DE 2007

CASTELLANOS & CO

ABOGADOS COLOMBIA

Calle 94A No. 7A-09- P.O.Box 6349 - Bogotá, Colombia
Tele.: (571) 610 74 20 / - Fax (571) 610 07 06 - e-mail info@castellanosyca.com



UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2. Has been signed by **Gregory John Taylor**
a été signé par
3. Acting in the capacity of **Notary Public**
agissant en qualité de
4. Bears the seal/stamp of **The Said Notary Public**
est revêtu du sceau/timbre de

Certified/Attesté

5. at London/à Londres

6. the/le **08 June 2007**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **H413882**

9. Stamp:
timbre:

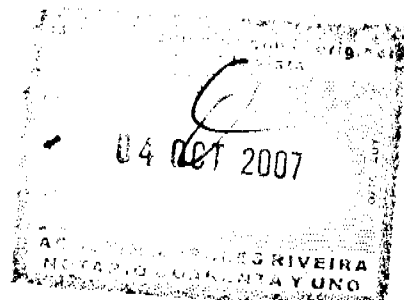
10. Signature: **J. Cooper**



Jh

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.



-----TRADUCCION OFICIAL No. 07-0705-----

De un documento escrito en INGLES, el cual para su identificación lleva el sello
y firma de la Traductora e Intérprete Oficial, Res. 2755/68 y 01144/97 de
Minjusticia.-----

(Anexos a un documento de cesión de patente de SYNGENTA
PARTICIPATIONS AG a favor de MERIAL LIMITED) Archivo No. 05.059.203
(fdo) ilegible

Gregory John Taylor

Notario Público

37 Meadway – Ashford Middlesex TW15 2TJ

Reino Unido

25 de Mayo de 2007

(Sello notarial en oblea ro)

APOSTILLA

(Convención de La Haya del 5 de Octubre de 1961)

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte

Este documento público

2. ha sido firmado por Gregory John Taylor

3. actuando en su carácter de Notario Público

4. lleva el sello de dicho Notario Público

Certificado

5. En Londres

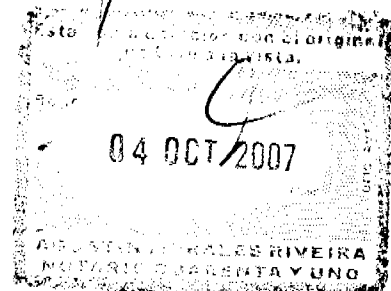
6. el día 8 de Junio de 2007

7. por el Secretario de Estado Principal de Su Majestad para Asuntos

Exteriores y de la Comunidad

8 No. H413882

DORA DUCHE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
RES. 2755/68 y 01144/97 - MINJUSTICIA
REG. DE COLECCION



9. Sello

10. Firma:

(fdo) ilegible

Por el Secretario de Estado

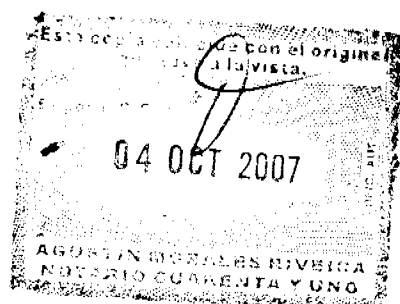
Si este documento es para ser usado en un país que no es miembro de la Convención de La Haya del 5 de Octubre de 1961, debe ser presentado ante la sección consular de la misión que represente ese país. Una apostilla o certificado de legalización sólo confirma que la firma, sello o estampado en el documento es auténtico. No significa que el contenido del documento sea correcto o que la Oficina de Asuntos Extranjeros o de la Comunidad aprueban el contenido.

ES TRADUCCION FIEL Y COMPLETA, a la cual me remito,

Bogotá, Julio 9, 2007



DORA DUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
RES. 02755/08 Y 01144/97 - MINJUSTICIA
REP. DE COLOMBIA



212

CASTELLANOS & CO LTDA
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

Señor

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E. S. D.

Ref.: **PODER** conferido por **MERIAL LIMITED**

Yo, **XIMENA CASTELLANOS ABONDANO**, mayor de edad, identificada y domiciliada como aparece al pié de mi firma, atentamente manifiesto a Uds. que sustituyo en la Dra. **MARGARITA CASTELLANOS ABONDANO**, el poder que me confirió **MERIAL LIMITED**, con domicilio en **3239 Satellite Blvd, Duluth, 30096-4640 Georgia, Estados Unidos de América**, debidamente legalizado por Apostilla bajo el No. **I-188150**, el día **20 de agosto de 2007**, con las mismas facultades que me fueron conferidas, para tramitar la solicitud de Patente PCT Entrada en Fase Nacional en Colombia, para: **"AVERMECTINA B1 Y DERIVADOS DE MONOSACARIDOS DE AVERMECTINA B1 QUE TIENEN UN SUSTITUYENTE ALCOXIMETILO EN LA POSICION 4" O 4'**, que se tramita bajo el Expediente No. **05.059.203**.

Del Señor Jefe,

Acepto


Ximena Castellanos Abondano
C.C. No. **39.773.330** de Usaquén
T.P.A. No. **58.236** del C.S.J.
Calle 94 A No. 7 A-09 – Bogotá
PBX: 610 74 20


Margarita Castellanos Abondano
C.C. No. **39.779.654** de Usaquén
T.P.A. No. **70.819** del C.S.J.
Calle 94 A No. 7 A-09 – Bogotá
PBX: 610 74 20

Bogotá, D.C.
XCA/MCA/jdf/4994-FNPCT

IDENTIFICACION DE FIRMA
MEDIANTE COMPARACION PERSONAL
(Art. 34 C.R.C. mod. Decr. 2282 de 1989, art. 1 mod. 36)
Act. del Notario Cuarenta y Uno (41) del círculo
de esta ciudad compareció personalmente:
Ximena Castellanos
Identificada con C.C. **39773330**
y tarjeta profesio-
nal de abogada No. **59256** del Consejo
de la Jurisdicción, con documento di-
S. I. C.

Ximena Castellanos



Firma del declarante

En Bogotá D.C. a **25 SET. 2007**
AUTORIZO ESTA DILIGENCIA EL SUSCRITO

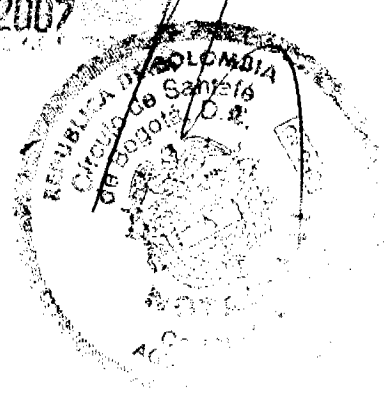
[Signature]

IDENTIFICACION DE FIRMA
MEDIANTE COMPARACION PERSONAL
(Art. 34 C.R.C. mod. Decr. 2282 de 1989, art. 1 mod. 36)
Act. del Notario Cuarenta y Uno (41) del círculo
de esta ciudad compareció personalmente:
Margante Castellanos
Identificada con C.C. **39779684**
y tarjeta profesio-
nal de abogada No. **70819** del Consejo
de la Jurisdicción, con documento di-
S. I. C.

Margante Castellanos



En Bogotá D.C. a **25 SET. 2007**
AUTORIZO ESTA DILIGENCIA EL SUSCRITO



COLOMBIA

PODER

El (los)

MERIAL LIMITED

Domiciliados en
3239 Satellite Blvd, Duluth, 30096-4640 Georgia, Estados
Unidos de América.

Nombran por el presente a **XIMENA CASTELLANOS A. y/o
MARGARITA CASTELLANOS A.** abogadas con oficinas en la
Calle 94A No. 7A-09, Bogotá-Colombia para

y para obtener la protección de mi (nuestra) propiedad
Industrial y con este fin autorizamos a dichos apoderados para
que nos representen ante cualesquiera autoridades o personas
de los órdenes administrativo, contencioso –administrativo y
judicial en todo lo relacionado con los siguientes actos y
gestiones:

- Obtención de patentes de invención, modelos y dibujos
industriales; registro de marcas de fabrica, de servicio,
colectivas o defensivas y de denominaciones de origen,
depósito de nombres y enseñas comerciales; su
renovación, prórroga, inscripción de traspaso y cambio de
nombre o domicilio, cancelación voluntaria y el registro de
licencias de uso de esos derechos;
- Para la obtención de registros sanitarios;
- Acciones de oposición, observación, cancelación, nulidad,
medidas cautelares y en general los juicios civiles, penales,
administrativos o contencioso - administrativos que
promovamos o se nos promuevan.

Pudiendo en todos los actos y gestiones arriba mencionados
sustituir éste mandato, transigir, desistir, recibir, cancelar,
renunciar, aceptar notificaciones y nombrar apoderados
judiciales y extrajudiciales.

Finalmente, este poder ratifica la validez de todos los actos y
solicitudes que, a nombre de la poderdante hubieren realizado
los apoderados en relación con las facultades anteriormente
enumeradas, antes de la suscripción del presente poder

Dado y firmado hoy Agosto 16, 2007

en Duluth, Georgia

por **MERIAL LIMITED**

(El notario debe suscribir el documento en la pagina siguiente)

(Se requiere legalización consular o mediante apostilla)

POWER OF ATTORNEY

I (we) the undersigned

MERIAL LIMITED

Of
3239 Satellite Blvd, Duluth, 30096-4640 Georgia, United
States of America.

hereby grant(s) Power of Attorney to **XIMENA
CASTELLANOS A. and /or MARGARITA CASTELLANOS A.**
attorneys residing at Calle 94A No. 7A-09, Bogotá- Colombia,
to

and to obtain the protection of my (our Industrial Property, for
which purpose we authorize the said attorneys to represent us
before any authorities, or persons, specially those,
administrative, contentious and judicial, in all matters
concerning the following:

- Obtainment of patents, models and designs, registration of
trademarks, service, collective and defensive marks, and of
designations of origin; the deposit of trade names and
ensigns; its renewal, extension, recordal of assignments,
change of name or domicile, voluntary cancellation, and the
registration of licenses of use of the above rights;
- For the obtainment of Sanitary registrations;
- Actions of opposition, cancellation, nullity, infringement,
granting of licenses; and in general the civil, criminal and
administrative suits related to those rights; actions and
suits instituted by us or against us;

In all the above matters they may substitute this power of
attorney, compromise, desist, cancel, receive, renounce,
accept notifications and appoint attorneys in fact, in or out of
court.

Finally, this power of attorney ratifies the validity of all acts
and applications made by the representatives in the name of
the signatory of this power of attorney, with regard to the
faculties above given, before the execution of the present
power of attc rey.

Given and signed this *16th day of August 2007*
in *Duluth, Georgia*

by 
(Notary shall execute on the other side)

(Consular legalization or apostille is required)

CASTELLANOS & CO

ABOGADOS COLOMBIA

Calle 94A No. 7A-09- P.O.Box 6349 - Bogotá, Colombia
Tels.: (571) 610 74 20 / - Fax (571) 610 07 06 - e-mail info@castellanosyco.com

Dora Patricia de Bernal
Trad. y Interprete Oficial
Reg 62705 68 y 71144/97 Minjusticia
Rep. de Colombia

25 SET 2007

R. VEIRA
AY JING

COLOMBIA

CERTIFICADO NOTARIAL (Sociedad)

Hoy 16 de 8 del año 2007
compareció (eron) personalmente
Judy Jarechi Black

a quienes conozco como la(s) personas que firma(n) en
representación de la Sociedad (Compañía) denominada

MERIAL LIMITED

Certifico :

a) Que
MERIAL LIMITED
es una sociedad/Compañía legalmente constituida y
existente de acuerdo con las leyes de Delaware

b) Que el domicilio de dicha Sociedad/Compañía es

3239 Satellite Blvd, Duluth, 30096-4640 Georgia, Estados
Unidos de América.

c) Que el objeto u objetos para los cuales se otorga el
presente poder están comprendidos dentro del objeto
social de la mencionada Sociedad /Compañía.

d) Que el Sr. Judy Jarechi Black
esta autorizado para otorgar el presente poder. Lo anterior
esta probado por medio de los siguientes documentos, que
certifico he visto*

Actas de la Junta Directiva de fecha
Julio 16, 2007
(Ciudad) Duluth,

(Estado) Georgia

Hoy 16 del Agosto, 2007

(Notario Público)

*Los documentos debe identificarse con fecha y origen.

NOTARIAL CERTIFICATION (Corporation)

On this 16th day of August of 2007
personally appeared

Judy Jarechi - Black

whom I know to be the person(s) who signed this document as
representative(s) of the Corporation /Company named

MERIAL LIMITED

I certify:

a) That
MERIAL LIMITED
is a corporation (Company legally constituted and in
existence in accordance with the laws of

Delaware

b) That the domicile of said Corporation/Company is
3239 Satellite Blvd, Duluth, 30096-4640 Georgia, United
States of America.

c) That the purpose or purposes for which the present
Power of Attorney is granted are comprised within the object
set forth in the charter of the mentioned
Corporation/Company.

d) That Mr. Dr. Judy Jarechi - Black
is (are) authorized to grant the present Power of Attorney. The
aforementioned was duly proven through the following
documents and I duly certify having seen them*:

Board Minutes dated July 16, 2007
(City) Duluth

(State) Georgia

this 16th day of August of the year 2007

J. Contreras

(Notary Public)

*Documents must be identified with date and origin

NOTARY PUBLIC, FULTON COUNTY, GEORGIA
MY COMMISSION EXPIRES MAY 3, 2008

CASTELLANOS & CO

ABOGADOS COLOMBIA

Calle 94A No. 7A-09- P.O.Box 6349 - Bogotá, Colombia

Tels.: (571) 810 74 20 / - Fax (571) 810 07 06 - e-mail info@castellanosyco.com

Dora Pineda de Bernal
Trad. Oficial
Esa 02765 08 y 01144, 97 Minjusticia
Rep. de Colombia

25 SET 2007

215

6003

**GEORGIA SUPERIOR COURT
CLERKS' COOPERATIVE AUTHORITY**

Notary Division
1875 Century Boulevard, Suite 100
Atlanta, Georgia 30345

APOSTILLE
(Convention de La Haye du 5 Octobre 1961)

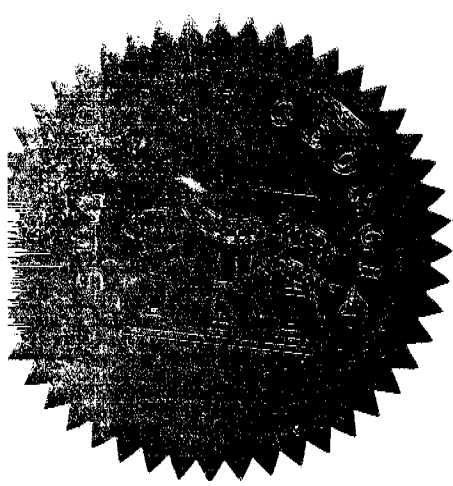
- 1. Country: **UNITED STATES OF AMERICA**
- 2. This public document
has been signed by **TIKI CANTRELL**
- 3. acting in the capacity of **NOTARY PUBLIC, STATE OF GEORGIA**
- 4. bears the seal/stamp of **TIKI CANTRELL
NOTARY PUBLIC
FULTON COUNTY, GEORGIA**

CERTIFIED

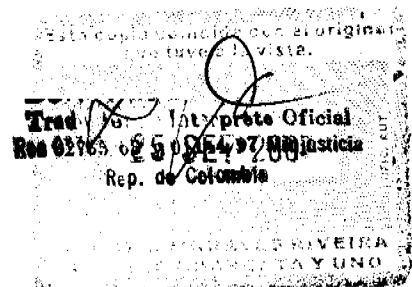
- 5. at **ATLANTA, GEORGIA**
- 6. the **20TH DAY OF AUGUST, 2007**
- 7. by **GEORGIA SUPERIOR COURT CLERKS' COOPERATIVE AUTHORITY**
- 8. No. **1-188150**
- 9. Seal/Stamp
- 10. Signature:

David R. Williams

**DAVID R. WILLIAMS
EXECUTIVE DIRECTOR**



**NOTARY PUBLIC
(404) 327-6023**



216

-----TRADUCCION OFICIAL No. 07-0912-----

De un documento escrito en INGLES, el cual para su identificación lleva el sello y firma de la Traductora e Intérprete Oficial, Res. 2755/68 y 01144/97 de Minjusticia.-----

(Anexos a un documento de Poder otorgado por Merial Limited)
(fdo) Tiki Cantrell

Sello: NOTARIO PUBLICO, CONDADO DE FULTON, GEORGIA

MI COMISION VENCE MAYO 3, 2008 (Sello en relieve)

APOSTILLA

(Convención de La Haya de Octubre 5, 1961)

1. Pais: Estados Unidos de América

Este documento público

2. ha sido firmado por: Tiki Cantrell

3. actuando en su carácter de: Notario Público, Estado de Georgia

4. lleva el sello de Tiki Cantrell, Notario Público, Condado de Fulton,
Georgia

CERTIFICADO:

5. en Atlanta, Georgia

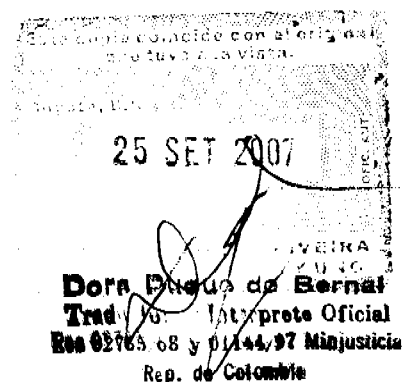
6. el día veinte de Agosto de 2007

7. por autoridad de la Cooperativa de Escribanos de la Corte
Superior de Georgia

8. No. 1-188150

9. Sello

10. Firma:

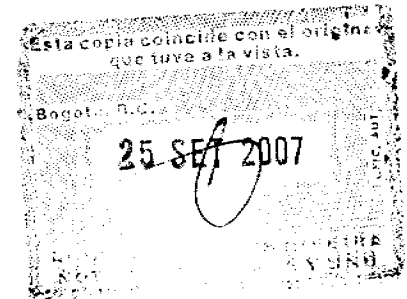


895265
Dora Duque
SECRETARIA DE
RELACIONES EXTERIORES
BOGOTA D.C.

RESPONSABILIDAD
DEL RECTOR

2007 SET 10 P 12:14
SECRETARIA DE
RELACIONES EXTERIORES
BOGOTA D.C.

MINISTERIO DE
RELACIONES EXTERIORES



217

(fdo) ilegible

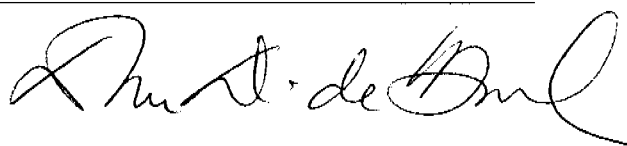
David R. Williams

Director Ejecutivo

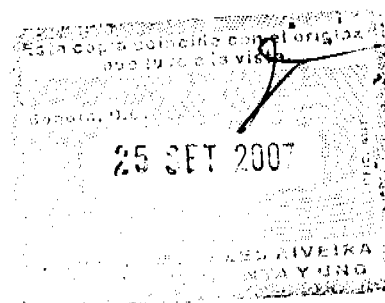
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ES TRADUCCION FIEL Y COMPLETA, a la cual me remito,

Bogotá, D. C., Septiembre 7, 2007



Dora Duque de Bernal
Traductora e Interpretadora
Rcn 02765/08 y 01144/87 en Bogotá
Rep. de Colombia



DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 05-59203

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **569** DE

FECHA **31 DE OCTUBRE DE 2006** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **01 DE FEBRERO 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

United States Patent [19]

Linn et al.

[11] Patent Number: 5,169,839
[45] Date of Patent: Dec. 8, 1992



US005169839A

[54] DERIVATIVES OF 3'- AND 3''-O-DESMETHYL AVERMECTIN COMPOUNDS, COMPOSITIONS AND METHODS OF TREATING MELMINTIC AND PARASITIC INFECTIONS

- [75] Inventors: Bruce O. Linn, Bridgewater; Helmut Mrozik, Matawan, both of N.J.
[73] Assignee: Merck & Co., Inc., Rahway, N.J.
[21] Appl. No.: 521,961
[22] Filed: May 11, 1990
[51] Int. Cl.⁵: A61K 31/70; C07H 17/04
[52] U.S. Cl.: 514/30; 536/7.1
[58] Field of Search: 536/7.1; 574/30

References Cited

U.S. PATENT DOCUMENTS

4,199,569	4/1980	Chabala et al.	514/30
4,201,861	5/1980	Mrozik et al.	536/7.1
4,289,760	9/1981	Mrozik et al.	514/30
4,427,663	1/1984	Mrozik et al.	514/30
4,997,383	1/1990	Sinclair	514/30

FOREIGN PATENT DOCUMENTS

375395 6/1990 European Pat. Off.

OTHER PUBLICATIONS

Schulman et al (I), *The Journal of Antibiotics* 38, pp. 1494-1498 (1988).
Schulman et al (II), *Antimicrobial Agents and Chemotherapy*, pp. 744-747 (1987).

Primary Examiner—Johnnie R. Brown
Assistant Examiner—Elli Peselev
Attorney, Agent, or Firm—David L. Rose; Joseph F. DiPrima

[57] ABSTRACT

There are disclosed derivatives of avermectin compounds wherein one or both of the 13-oleandrose saccharide groups lack the methyl group of the 3'- or 3''-methoxy. Such compounds are potent anthelmintic and antiparasitic agents.

10 Claims, No Drawings

DERIVATIVES OF 3'- AND 3''-O-DESMETHYL AVERMECTIN COMPOUNDS, COMPOSITIONS AND METHODS OF TREATING MELMINTIC AND PARASITIC INFECTIONS

BACKGROUND OF THE INVENTION

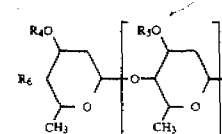
Desmethyl avermectin compounds wherein one or both of the oleandrose saccharide groups are demethylated are disclosed in Schulman et. al. in *The Journal of Antibiotics*, 38, 1494-1498 (1985). Such compounds are natural products produced by the fermentation of a strain of *Streptomyces avermectilis* in the presence of sinefungin. The instant compounds are derivatives of the compounds disclosed in Schulman et. al. Other avermectins missing one or both of the 3'-O- and 3''-O-methyl groups are disclosed in EPO published application 276131, and derivatives of these compounds are also used as starting materials for the compounds of this invention. It is known from Schulman et. al. that such avermectin derivatives missing one or both of the 3'-O- and 3''-O-methyl groups have reduced potency as anthelmintic agents. However certain derivatives obtained through chemical modification of these compounds have highly potent antiparasitic and insecticidal activity.

SUMMARY OF THE INVENTION

This invention is concerned with novel avermectin compounds derived from 3'- and 3''-O-desmethyl starting materials. Thus, it is an object of this invention to describe such compounds and processes for their preparation. A further object of this invention is to describe the use of such compounds in the treatment of parasitic infections. A still further object of this invention is to describe compositions for such use using the described compounds as the active agent thereof. Further objects will become apparent from a reading of the following description.

DESCRIPTION OF THE INVENTION

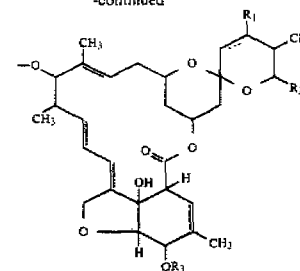
The novel compounds of the instant invention are best realized in the following structural formula.



5,169,839

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-continued



wherein the broken line at the 22,23 positions indicates that either a single or a double bond is present at the 22,23 position and that R₁ is present only when the broken line indicates a 22,23-single bond;

- n is 0 or 1;
R₁ is hydrogen, hydroxy or a 23-oxo group;
R₂ is an α -branched C₃-C₈ alkyl, alkenyl, alkoxyalkyl or alkylthioalkyl; a C₄-C₈ cycloalkyl C₁-C₄ alkyl group, a C₃-C₈ cycloalkoxy or a C₃-C₈ cycloalkenyl, each of which may be optionally substituted by methylene, or one or more C₁-C₄ alkyl groups or halogen; or a 3 to 6 membered oxygen or sulfur containing heterocycle which may be saturated or fully or partly unsaturated and which may be substituted by one or more C₁-C₄ alkyl groups or halogen atoms;
R₃ is hydrogen, methyl, loweralkanoyl, loweralkyl-carbonyl, or trimeralkylsilyl;
R₄ and R₅ are independently hydrogen, methyl, loweralkanoyl, benzoyl, loweralkoxy carbonyl, phenoxycarbonyl, carbamoyl, N-loweralkyl carbamoyl, or N,N-diloweralkylcarbamoyl or loweralkoxyloweralkyl, provided that both R₄ and R₅ are hydrogen only when R₆ is other than hydroxy and provided that both R₄ and R₅ are not simultaneously methyl; and
R₆, with the broken line indicating a single bond to R₆ is hydroxy, amino, N-loweralkylamino, N,N-diloweralkylamino, loweralkanoylamino, N-loweralkanoyl-N-loweralkylamino, loweralkoxycarbonylamino, trimeralkylsilyloxy, carbamoyloxy, N-lower-alkylcarbamoyloxy, N,N-diloweralkyl carbamoyloxy, loweralkoxymethoxy, loweralk-anoyloxy, substituted loweralkanoyloxy such as succinoyloxy or acetylglucyloxy, or when the broken line indicates a double bond to R₆, R₆ is oxo, semicarbazono, loweralkanoyl hydrazono, benzoyl hydrazono, loweralkyl substituted benzoyl hydrazono or p-toluene sulfonylhydrazono;
Preferred compounds of this invention are realized in the foregoing structural formula when:
R₁ is hydrogen or hydroxy;
R₂ is an α -branched C₃-C₈ alkyl or alkenyl group;
R₃ is hydrogen or methyl;
R₄ and R₅ are independently hydrogen, methyl, loweralkanoyl, benzoyl, loweralkoxycarbonyl, loweralkoxyloweralkyl provided that both R₄ and R₅ are hydrogen only when R₆ is other than hydroxy and provided that both R₄ and R₅ are not simultaneously methyl; and

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b.19

R₄, with the broken line indicating a single bond, is hydroxy, amino, N-loweralkylamino, N,N-diloweralkylamino, loweralkoxylamino, N-loweralkoxyl-N-loweralkylamino, loweralkoxymethoxy or loweralkoxyloxy.

Additional preferred compounds of this invention are realized in the foregoing structural formula when:

R₁ is hydrogen or hydroxy;

R₂ is 2-propyl, 2-butyl, 2-pentyl, 2-hexyl, 2-buten-2-yl, 2-penten-2-yl, 4-methyl-2-penten-2-yl, cyclohexyl, cyclopentyl, 3-thienyl, 3-furyl, 1-methylthioethyl;

R₃ is hydrogen;

R₄ and R₅ are independently hydrogen, methyl, loweralkanyl, loweralkoxyloweralkyl, loweralkoxycarbonyl, carbamoyl, N-loweralkylcarbamoyl, N,N-diloweralkylcarbamoyl, provided that both R₄ and R₅ are hydrogen only when R₄ is other than hydroxy provided that both R₄ and R₅ are not simultaneously methyl; and;

R₆, with the broken line indicating a single bond, is hydroxy, amino, N-methylamino, N,N-dimethylamino, acetylamino, ethoxymethoxy, acetoxy, succinoyloxy or acetylglucyloxy.

Additional preferred compounds, are realized when both R₄ and R₅ are other than hydrogen or methyl.

Preferred compounds of the instant invention are further realized in the following compounds:

3''-O-desmethyl-3',4''-di-O-acetyl avermectin B1a/B1b;

3''-O-desmethyl avermectin B1a/B1b 3',4''-O-carbonate ester;

3''-O-desmethyl-4''-O-succinoyl avermectin B1a/B1b;

4''-O-(acetylglucyl)-3''-O-desmethyl avermectin B1a/B1b;

3''-O-desmethyl-4''-O-[(dimethylamino)carbonyl] avermectin B1a/B1b;

3''-O-desmethyl-4''-deoxy-4''-(methylamino) avermectin B1a/B1b;

3''-O-desmethyl-4''-deoxy-4''-epi(methylamino) avermectin B1a/B1b;

3',3''-O-bis-desmethyl-3',4''-di-O-methoxymethyl avermectin B1a/B1b;

3',3''-bis-O-desmethyl-25-cyclohexyl-25-de-(2-butyl)-3',4''-di-O-methoxymethyl avermectin B2a;

3',3''-bis-O-desmethyl-25-cyclopentyl-25-de-(2-butyl)-3',4''-di-O-methoxymethyl avermectin B2a;

3',3''-bis-O-desmethyl-25-(3-thienyl)-25-de-(2-butyl)-3',4''-di-O-methoxymethyl avermectin B2a;

3',3''-bis-O-desmethyl-25-(3-furyl)-25-de-(2-butyl)-3',4''-di-O-methoxymethyl avermectin B2a;

3',3''-bis-O-desmethyl-25-(1-methylthioethyl)-25-de-(2-butyl)-3',4''-di-O-methoxymethyl avermectin B1a;

3''-acetyl amino-3''-deoxy-3',3''-bis-O-desmethyl-3',4''-di-O-methoxymethyl avermectin B1a/B1b;

4''-O-acetyl-3',3''-bis-O-desmethyl avermectin B1a/B1b;

3''-O-desmethyl avermectin B1a/B1b monosaccharide;

3''-O-desmethyl-4''-O-methoxymethyl avermectin B1a/B1b monosaccharide.

In the instant description of the invention, the term "loweralkyl" is intended to include those alkyl groups of from 1 to 6 carbon atoms in either a straight or branched configuration. Examples of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, pentyl, hexyl and the like.

The term loweralkoxy is intended to include those alkoxy groups of from 1 to 6 carbon atoms in either a straight or branched configuration. Examples of such

alkoxy groups are methoxy, ethoxy, propoxy, butoxy, tertbutoxy, pentoxy, hexoxy and the like.

The term "loweralkanoyl" is intended to include those alkanoyl groups containing from 1 to 6 carbon atoms in either a straight or branched configuration. Examples of such alkanoyl groups are formyl, acetyl, propyl, butyryl, isobutyryl, pentanoyl, hexanoyl and the like. Preparation of starting materials.

The compounds used as starting materials for the instant invention are produced through artificial modification of the fermentation of *Streptomyces avermitilis* either by addition of metabolic inhibitors such as cinnofungin (as described by Schulman et al., *J. Antibiot.* 1985, 38, 1494-1498) or by mutation of the parent strain (as described by Schulman et al., *Antimicrobial Agents and Chemotherapy*, 1987, 31, 744-747, and by EP-276-131-A to Pfizer Inc.). Avermectin derivatives missing one or two of the 3'- and 3''-O-methyl groups have reduced anthelmintic potencies (Schulman et al., *J. Antibiot.* 1985, 38, 1494-1498). It was now found that derivatives of such 3'- or 3''-O-desmethyl avermectin, derivatives, however, are very potent anthelmintic agents.

The instant compounds with an acyl function at the 5, 4', 4'', 3', 3'', or 23 positions are prepared by acylating the various hydroxy groups at such positions of the 3'- or 3''-O-desmethyl avermectin compounds. In particular the 5-hydroxy, 4'-hydroxy, 4''-hydroxy, 3'-hydroxy, 3''-hydroxy or the 23-hydroxy groups can be reacted with acylating agents to prepare the appropriate acylated derivative, such as the loweralkanoyl, benzoyl, loweralkoxycarbonyl, phenoxycarbonyl, carbamoyl, N-loweralkylcarbamoyl, and N-diloweralkylcarbamoyl substituents. 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. Pat. No. 4,201,861 to Mrozik et al. The 23-hydroxy group is more difficult to acylate and usually needs forcing conditions for its acylation. Thus it does not usually need to be protected when reacting other hydroxy groups on the molecule.

In addition, those compounds with a 23-keto function are prepared by the selective oxidation of the 23-hydroxy group with pyridinium dichromate, chromic acid-dimethyl pyrazole, and the like as disclosed in U.S. Pat. No. 4,289,760 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 Wilkinsons homogeneous catalyst, triphenylphosphine rhodium chloride is described in U.S. Pat. No. 4,199,569 to Chabala et al.

The reactions which produce the various 4'' or 4' derivatives such as the keto, amino and substituted amino involve 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. These processes are detailed in U.S. Pat. No. 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, 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.

It is very often desirable to protect those reactive groups which are not intended to be reacted and it has

been found that the trisubstituted silyl group is preferred, in particular tri-butyl-dimethylsilyl. The protected compounds are, however, significantly active anthelmintic agents and such silyl derivatives are intended to be within the ambit of this invention. The procedures for the preparation of such compounds is described in the foregoing cited patents.

The "b" compounds, those with a 25-iso-propyl group, may be somewhat difficult to separate from the corresponding "a" compound with a 25-sec-butyl group and as such the compounds are generally isolated as mixtures of the two compounds. Thus references in the instant application to "a" compounds such as B1a, A1a, and the like, are construed to actually contain a certain proportion of the corresponding "b" compound. Alternatively, this representation of a mixture is sometimes done by referring to the B1 or B2 compounds without specifically designating "a" or "b" compounds, or by separating the "a" compound from the "b" compound by a slash (/) such as B1a/B1b, B2a/B2b and the like.

The novel compounds of this invention have significant parasitocidal activity as anthelmintics, ectoparasitocides, 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 substituted 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. The compounds are active against other plant pests such as the southern army worm and Mexican bean beetle larvae.

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. Generally, 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 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 the active compound.

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EXAMPLE 20

3',3'-Bis-O-desmethyl-3',4'-di-O-methoxymethylavermectin B1a/B1b

A solution of 3',5-tert-butylidimethylsilyl-3',3'-bis-O-desmethyl-3',4'-di-O-methoxymethylavermectin B1a/B1b, 33 mg, in 1.5 mL of anhydrous hydrogen fluoride-pyridine in tetrahydrofuran solution as described in EXAMPLE 5 was stirred at room temperature, 23° C., for 11 hours. Then aqueous sodium bicarbonate solution was added with stirring, and the product was extracted with methylene chloride. The methylene chloride solution was extracted with aqueous sodium bicarbonate, dried over sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel plates using methylene chloride-methanol (97:3) furnishing 25.6 mg of 3',3'-bis-O-desmethyl-3',4'-di-O-methoxymethylavermectin B1a/B1b [939 (M+L)⁺], which was fully characterized by nuclear magnetic resonance, mass spectra and high pressure liquid chromatographic analyses.

EXAMPLE 20a

If one uses the compounds (1a) through (5a) obtained as described fully in EP 276-131-A as starting materials for the procedure of EXAMPLE 18 and follows the procedures as described in EXAMPLES 18, 19, and 20, the products (1b) through (5b) are obtained:

Starting materials:

- 1a) 3',3'-Bis-O-desmethyl-25-cyclohexyl-25-de-(2-butyl)avermectin B2a
- 2a) 3',3'-Bis-O-desmethyl-25-cyclopentyl-25-de-(2-butyl)avermectin B2a
- 3a) 3',3'-Bis-O-desmethyl-25-(3-thienyl)-25-de-(2-butyl)avermectin B2a
- 4a) 3',3'-Bis-O-desmethyl-25-(3-furyl)-25-de-(2-butyl)avermectin B2a
- 5a) 3',3'-Bis-O-desmethyl-25-(1-methylthioethyl)-25-de-(2-butyl)avermectin B1a

Reaction Products:

- 1b) 3',3'-Bis-O-desmethyl-25-cyclohexyl-25-de-(2-butyl)-3',4'-di-O-methoxymethylavermectin B2a
- 2b) 3',3'-Bis-O-desmethyl-25-cyclopentyl-25-de-(2-butyl)-3',4'-di-O-methoxymethylavermectin B2a
- 3b) 3',3'-Bis-O-desmethyl-25-(3-thienyl)-25-de-(2-butyl)-3',4'-di-O-methoxymethylavermectin B2a
- 4b) 3',3'-Bis-O-desmethyl-25-(3-furyl)-25-de-(2-butyl)-3',4'-di-O-methoxymethylavermectin B2a
- 5b) 3',3'-Bis-O-desmethyl-25-(1-methylthioethyl)-25-de-(2-butyl)-3',4'-di-O-methoxymethylavermectin B1a

EXAMPLE 21

5'-O-tert-Butyldimethylsilyl-3',3'-bis-O-desmethyl-3',4'-di-O-methoxymethylavermectin B1a/B1b

A solution containing 240 mg of 3',3'-bis-O-desmethyl-3',4'-di-O-methoxymethylavermectin B1a/B1b, 47 mg of imidazole, and 52 mg of tert-butyldimethylsilyl chloride in 2.0 ml of dimethylformamide is stirred at room temperature for 45 minutes according to the procedure of EXAMPLE 1. Purification by preparative silica gel layer chromatography gives 5'-O-tert-butyl-21 dimethylsilyl-3',3'-bis-O-desmethyl-3',4'-di-O-methoxymethylavermectin B1a/B1b, which is characterized by its mass and NMR spectra.

EXAMPLE 22

5'-O-tert-Butyldimethylsilyl-3',3'-bis-O-desmethyl-3',4'-di-O-methoxymethyl-3'-oxoavermectin B1a/B1b

96 mg of 5'-O-tert-butylidimethylsilyl-3',3'-bis-O-desmethyl-3',4'-di-O-methoxymethylavermectin B1a is reacted according to the procedure of EXAMPLE 14 with 20 microliter of oxalyl chloride, 32 microliter of dimethylsulfoxide, and 0.15 ml of triethylamine in methylene chloride give the title compound, which is characterized by its mass and NMR spectra.

EXAMPLE 23

3'-Amino-3'-deoxy-5'-O-tert-Butyldimethylsilyl-3',3'-bis-O-desmethyl-3',4'-di-O-methoxymethylavermectin B1a/B1b

A solution of 210 mg of 5'-O-tert-butylidimethylsilyl-3',3'-bis-O-desmethyl-3',4'-di-O-methoxymethyl-3'-oxoavermectin B1a/B1b and of 160 mg of ammonium acetate in 2.0 ml of methanol is reacted with 12 mg of sodium cyanoborohydride at room temperature for 100 minutes. Then 10 ml of an aqueous one half saturated sodium carbonate solution is added and the products are extracted with ethylacetate. The ethylacetate extract is washed with water, dried over magnesium sulfate, and concentrated in vacuo to a yellow glass. Purification by preparative silica gel layer chromatography gives 3'-amino-3'-deoxy-5'-O-tert-butylidimethylsilyl-3',3'-bis-O-desmethyl-3',4'-di-O-methoxymethylavermectin B1a/B1b, which is characterized by its mass and NMR spectra.

EXAMPLE 24

3'-Acetylamino-3'-deoxy-5'-O-tert-butylidimethylsilyl-3',3'-bis-O-desmethyl-3',4'-di-O-methoxymethylavermectin B1a/B1b

A solution of 145 mg of 3'-amino-3'-deoxy-5'-O-tert-butylidimethylsilyl-3',3'-bis-O-desmethyl-3',4'-di-O-methoxymethylavermectin B1a in 1.25 ml of CH₂Cl₂ is treated with 16 microliter (17 mg, 1.2 equivalents) of acetic anhydride and kept at room temperature for 1 hour. Then the reaction mixture is diluted with ethyl acetate, washed with aqueous sodium bicarbonate and water, dried and concentrated in vacuo to a foam. Purification by preparative silica gel layer chromatography gives 3'-acetylamino-3'-deoxy-5'-O-tert-butylidimethylsilyl-3',3'-bis-O-desmethyl-3',4'-di-O-methoxymethylavermectin B1a/B1b, which is characterized by its mass and NMR spectra.

EXAMPLE 25

3'-Acetylamino-3'-deoxy-3',3'-bis-O-desmethyl-3',4'-di-O-methoxymethylavermectin B1a/B1b

A solution 55 mg of 3'-acetylamino-3'-deoxy-5'-O-tert-butylidimethylsilyl-3',3'-bis-O-desmethyl-3',4'-di-O-methoxymethylavermectin B1a/B1b is deprotected with 50 mg of p-toluenesulfonic acid monohydrate in 5.0 ml of methanol according to the procedure of EXAMPLE 3 to give 3'-acetylamino-3'-deoxy-3',3'-bis-O-desmethyl-3',4'-di-O-methoxymethylavermectin B1a/B1b, which is characterized by its mass and NMR spectra.

EXAMPLE 26

4'-O-Acetyl-3',3'-tri-O-tert-butylidimethylsilyl-3',3'-bis-O-desmethylavermectin B1a/B1b

A solution of 3',3',5-tri-O-tert-butylidimethylsilyl-3',3'-bis-O-desmethylavermectin B1a/B1b, 55 mg, in 1.0 mL of pyridine and 0.5 mL of acetic anhydride was stirred at room temperature, 23° C., for 18 hours. The reaction solution was diluted with toluene and then concentrated under reduced pressure. The residue was taken up in methylene chloride, and the solution was washed with aqueous sodium bicarbonate, dried over sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica gel plates furnishing 41 mg of 4'-O-acetyl-3',3',5-tri-O-tert-butylidimethylsilyl-3',3'-bis-O-desmethylavermectin B1a/B1b [1235(M+L)⁺] which was characterized by nuclear magnetic resonance, mass spectra and high pressure liquid chromatographic analyses.

EXAMPLE 27

4'-O-Acetyl-3',3'-bis-O-desmethylavermectin B1a/B1b

4'-O-Acetyl-3',3'-tri-O-tert-butylidimethylsilyl-3',3'-bis-O-desmethylavermectin B1a/B1b, 24 mg, was treated with 0.8 mL of anhydrous hydrogen fluoride-pyridine tetrahydrofuran as described in EXAMPLES 5 and 20. The residue from the methylene chloride solution was chromatographed on silica gel plates using methylene chloride-methanol (95:5) furnishing 7.5 mg of 4'-O-acetyl-3',3'-bis-O-desmethylavermectin B1a/B1b, [887(M+H)⁺], which was characterized by nuclear magnetic resonance, mass spectra and high pressure liquid chromatographic analyses.

EXAMPLE 28

3'-O-Desmethylavermectin B1a/B1b monosaccharide

A solution containing 2.11 g of 3',3'-bis-O-desmethylavermectin B1a/B1b in 20 ml of tetrahydrofuran is added slowly to a mixture of 4.6 ml of water, 4.6 ml of sulfuric acid and 17 ml of tetrahydrofuran stirred in an ice bath. The reaction mixture is left at room temperature for 18 hours, cooled again and poured onto ice and water. Extraction with methylenechloride, washing with aqueous sodium bicarbonate and water, drying and concentrated in vacuo gives a brown foam. Silica gel column chromatography with methylenechloride-ethyl acetate solvent mixtures gives avermectin B1a/B1b aglycone and the desired 3'-O-desmethylavermectin B1a/B1b monosaccharide, which is characterized by its mass and NMR spectra.

EXAMPLE 29

3'-O-Desmethyl-3',5-di-O-tert-butylidimethylsilyl-avermectin B1a/B1b monosaccharide

3'-O-Desmethyl-3',5-di-O-tert-butylidimethylsilyl-avermectin B1a/B1b monosaccharide is obtained when 3'-O-desmethylavermectin B1a/B1b monosaccharide is reacted according to the procedure of EXAMPLE 18, and is characterized by its mass and NMR spectra.

EXAMPLE 30

3'-O-Desmethyl-3',5-di-O-tert-butylidimethylsilyl-4'-O-methoxymethylavermectin B1a/B1b monosaccharide

3'-O-Desmethyl-3',5-di-O-tert-butylidimethylsilyl-4'-O-methoxymethylavermectin B1a/B1b monosaccharide

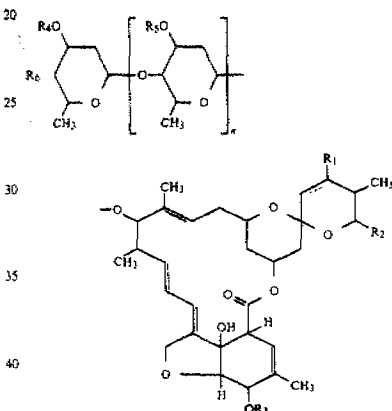
ride is obtained when 3'-O-desmethyl-3',5-di-O-tert-butylidimethylsilyl-4'-O-methoxymethylavermectin B1a/B1b monosaccharide is reacted according to the procedure of EXAMPLE 19, and is characterized by its mass and NMR spectra.

EXAMPLE 31

3'-O-Desmethyl-4'-O-methoxymethylavermectin B1a/B1b monosaccharide

3'-O-Desmethyl-4'-O-methoxymethylavermectin B1a/B1b monosaccharide is obtained when 3'-O-desmethyl-3',5-di-O-tert-butylidimethylsilyl-4'-O-methoxymethyl-avermectin B1a/B1b monosaccharide is reacted according to the procedure of EXAMPLE 20, and is characterized by its mass and NMR spectra. What is claimed is:

1. A compound having the formula:



wherein the broken line at the 22,23 positions indicates that either a single or a double bond is present at the 22,23 position and that R₁ is present only when the broken line indicates a 22,23-single bond; n is 0 or 1;

R₁ is hydrogen, hydroxy or a 23-oxo group;

R₂ is an α-branched C₃-C₈ alkyl, alkenyl, alkoxyalkyl or alkylthioalkyl; a C₃-C₈ cycloalkyl C₁-C₄ alkyl group, a C₃-C₈ cycloalkyl or a C₃-C₈ cycloalkenyl, each of which may be optionally substituted by methylene, or one or more C₁-C₄ alkyl groups or halogen; or a 3 to 6 membered oxygen or sulfur containing heterocycle which may be saturated or fully or partly unsaturated and which may be substituted by one or more C₁-C₄ alkyl groups or halogen atoms;

R₃ is hydrogen, methyl, loweralkanoyl, loweralkoxycarbonyl, or loweralkylsilyl;

R₄ and R₅ are independently hydrogen, methyl, loweralkanoyl, benzoyl, loweralkoxycarbonyl, phenoxycarbonyl, carbamoyl, N-loweralkylcarbamoyl, N,N-diloweralkyl-carbamoyl or loweralkoxy loweralkyl, provided that both R₄ and R₅ are not simultaneously methyl; and

R₆, with the broken line indicating a single bond to R₆ is N-loweralkanoyl-N-loweralkylamino, loweralkoxycarbonylamino, trioweralkylsilyloxy, loweralkoxymethoxy, succinoyloxy or acetyl-glycyloxy, or, when the broken line indicates a double bond to R₆, R₆ is, semicarbazono, loweralkanoyl hydrazono, benzoyl hydrazono, loweralkyl substituted benzoyl hydrazono or p-toluene sulfonylhydrazono.

2. The compounds of claim 1 wherein:

R₁ is hydrogen or hydroxy;

R₂ is an alpha-branched C₃-C₈ alkyl or alkenyl group; and

R₃ is hydrogen or methyl;

R₄ and R₅ are independently hydrogen, methyl, loweralkanoyl, benzoyl, loweralkoxycarbonyl or loweralkoxyloweralkyl provided that both R₄ and R₅ are not simultaneously methyl; and

R₆, with the broken line indicating a single bond is, N-loweralkanoyl-N-loweralkylamino or loweralkoxymethoxy.

3. The compounds of claim 1 wherein

R₁ is hydrogen or hydroxy;

R₂ is 2-propyl, 2-butyl, 2-pentyl, 2-hexyl, 2-buten-2-yl, 2-penten-2-yl, 4-methyl-2-penten-2-yl, cyclohexyl, cyclopentyl, 3-thienyl, 3-furyl or 1-methylthioethyl;

R₃ is hydrogen;

R₄ and R₅ are independently hydrogen, methyl, loweralkanoyl, loweralkoxyloweralkyl, loweralkox-

ycarbonyl, carbamoyl, N-loweralkylcarbamoyl or N,N-diloweralkylcarbamoyl, provided that both R₄ and R₅ are not simultaneously methyl; and;

R₆, with broken line indicating a single bond, is ethoxymethoxy, succinoyloxy, or acetyl-glycyloxy.

4. The compounds of claim 1 wherein both R₄ and R₅ are other than hydrogen or methyl.

5. The compound of claim 3 which is 3',3"-bis-O-desmethyl-3',4"-di-O-methoxymethyl avermectin B1a/B1b.

6. The compound of claim 3 which is 3"-O-desmethyl-22,23-dihydro-4"-O-methoxymethyl avermectin B1a/B1b.

7. The compound of claim 3 which is 3"-acetylaminomethyl-3',3"-bis-O-desmethyl-3',4"-di-O-methoxymethyl avermectin B1a/B1b.

8. A method for the treatment of helminthic or parasitic infections in animals infected with helminths or parasites which comprises administering to such animals an effective amount of a compound of claim 1.

9. A method for the treatment of parasites of plants infected with parasites which comprises applying to such plants, to the soil in which they grow, or to the crops harvested therefrom, and effective amount of a compound of claim 1.

10. A composition useful for the treatment of parasitic diseases of plants or animals which comprises an inert carrier and an effective amount of a compound of claim 1.

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[54] NOVEL SUBSTANCES AND PROCESS FOR THEIR PRODUCTION

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[21] Appl. No.: 948,682

[22] Filed: Sep. 8, 1978

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 874,607, Feb. 2, 1978, abandoned, which is a continuation-in-part of Ser. No. 772,601, Mar. 2, 1977, abandoned, which is a continuation-in-part of Ser. No. 678,328, Apr. 19, 1976, abandoned.

[51] Int. Cl.³ A61K 31/71; C07H 17/08

[52] U.S. Cl. 424/181; 435/76; 435/119; 435/253; 260/343.41; 536/17 R

[58] Field of Search 424/180, 181; 536/17 R, 536/17 C

[56]

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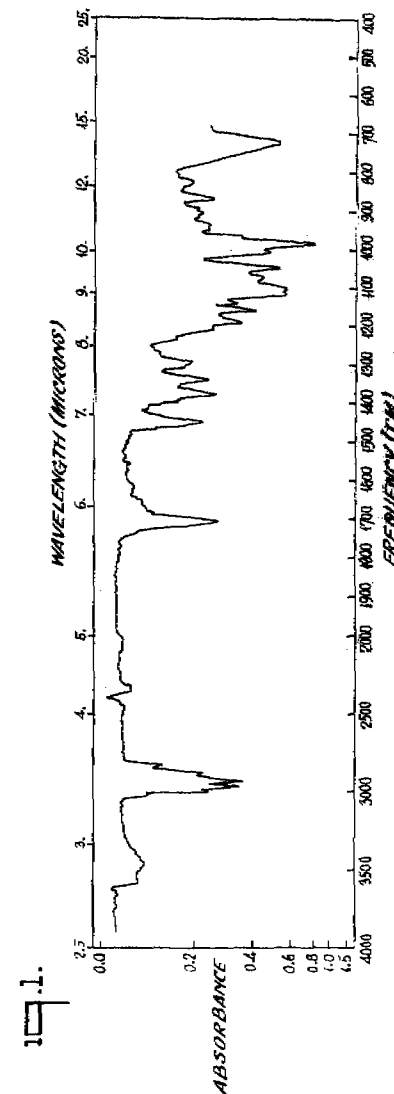
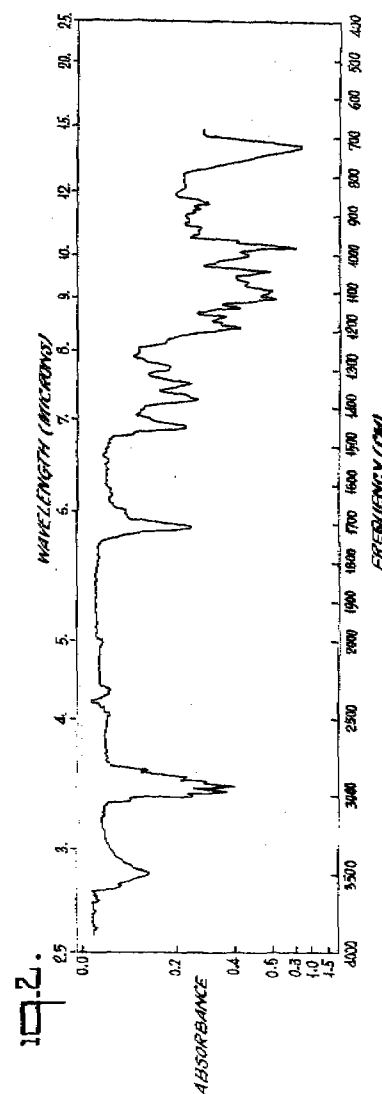
Primary Examiner—Johnnie R. Brown
Attorney, Agent, or Firm—David L. Rose; Harry E. Westlake

[57]

ABSTRACT

Novel compounds are produced by the fermentation of a nutrient medium with the previously undescribed microorganism *Streptomyces avermitilis*. They may be isolated by solvent extraction and chromatographic fractionation techniques. The compounds, which are described generically as C-076 have significant parasitidal activity. The compounds may be included in compositions for the oral or parenteral administration to animals for the treatment of parasitic infections.

14 Claims, 8 Drawing Figures



5.22.10

to remove the organic solvent and extracted several times with a second solvent. When the first extraction employs a water miscible solvent, the second extraction preferably employs a water immiscible solvent such as chloroform, methylene chloride, carbon tetrachloride,

terizes the degree and nature of unsaturation present in the particular compound. The optical rotations were determined using standard techniques with a Karl Zeiss polarimeter. The concentration factor (c) is given as a percent of the compound in the stated solvent.

TABLE I

	A1a	A1b	A2a	A2b	B1a	B1b	B2a	B2b
Molecular Formula	C ₂₉ H ₄₂ O ₁₄	C ₂₉ H ₄₂ O ₁₄	C ₂₉ H ₄₂ O ₁₅	C ₂₉ H ₄₂ O ₁₅	C ₂₉ H ₄₂ O ₁₄	C ₂₉ H ₄₂ O ₁₄	C ₂₉ H ₄₂ O ₁₅	C ₂₉ H ₄₂ O ₁₅
Optical Rotation	+68.5° ± 2° (C = 0.77)		+48.8° ± 2° (C = 1.64)		-55.7° ± 2° (C = 1.06)		+38.3° ± 2° (C = 0.87)	
[α] _D ²⁵ (CHCl ₃)	886	872	904	890	872	858	890	876
Molecular Weight (Determined by mass spectrometry)	237		237		237		237	
Ultraviolet	(28,700)		(28,800)		(29,120)		(27,580)	
Absorption	4.458		4.459		4.464		4.441	
Spectrum	243		243		243		243	
λ-max(mμ)	(31,275)		(31,740)		(31,850)		(30,590)	
(ε, loge)	4.495		4.501		4.503		4.486	
	252		252		252		252	
	(20,290)		(20,425)		(20,510)		(20,060)	
	4.307		4.310		4.313		4.302	

ethylacetate, methyl ethyl ketone, methylisobutyl ketone and the like. These latter extracts are dried and concentrated using known techniques to afford a residue comprising C-076 admixed with other materials. This fraction is then conveniently chromatographed in order to separate the active C-076 compounds from other material and also to separate and isolate the individual C-076 compounds. The chromatographic techniques which may be employed to purify the C-076 compounds are generally known to those skilled in this art. Examples of such techniques are column chromatography, using such media as silica gel, aluminum oxide, dextran gels and the like, and elution of such columns with various solvents, and/or a combination of two or more solvents, in varying ratios. Liquid chromatography is employed for the detection of the C-076 compounds, and high pressure liquid chromatography may be employed to isolate purified fractions containing one or more of such compounds. Likewise, thin layer chromatography may be employed to detect the presence of, and to isolate the individual C-076 compounds. The use of the foregoing techniques as well as others known to those skilled in this art, will afford purified compositions comprising the C-076 compounds as well as the individual C-076 compounds themselves. The presence of the active C-076 compounds is determined by analyzing the various chromatographic fractions for antiparasitic activity and also by the spectral characteristics (such as ultraviolet and infrared) of said compounds as described below.

The spectral and other physical-chemical characteristics of the individual C-076 compounds are set forth in tabular form in Table I. These compounds are very soluble in most common organic solvents, and are of minimal solubility in water.

The ultraviolet spectral data in Table I were obtained on a Cary Model 15 Ultraviolet Spectrometer in methanol solutions in 1 cm. quartz cells. The concentration of the compound was approximately 25 μg/ml. The ultraviolet absorption, while represented as that of a particular "a series" compound, is actually the absorption of the "a series" compound which contains a minor amount of a "b series" compound. The "a" and "b" series differ only by a -CH₂-moiety in a lower alkyl substituent which difference is not associated with the chromophore. Ultraviolet absorption primarily charac-

terizes the degree and nature of unsaturation present in the particular compound. The optical rotations were determined using standard techniques with a Karl Zeiss polarimeter. The concentration factor (c) is given as a percent of the compound in the stated solvent.

TABLE II

A1 (0.6 ml. 16%)	
12.0, 13.0, 15.1, 16.4, 17.7, 18.4, 19.9, 20.3, 27.5, 30.6, 34.3 (3C), 35.2, 36.6, 39.7, 40.5, 45.7, 56.4 (2C), 57.7, 67.3, 68.2 (2C), 68.4 (2C), 74.9, 76.1, 77.0, 77.5, 78.3, 79.4, 80.6 (2C), 82.0, 95.0, 95.8, 98.5, 118.4 (2C), 119.7, 124.9, 127.8, 135.2, 136.0, 136.1, 137.6, 139.5, 173.8.	
A2 (0.6 ml. 16%)	
11.8, 12.4, 13.8, 15.1, 17.7, 18.4, 19.9, 20.3, 27.5, 34.3 (3C), 35.2, 35.8, 36.5, 39.8, 40.8, 41.2, 45.7, 56.4 (2C), 57.7, 67.3, 67.7, 68.2 (3C), 69.9, 70.8, 76.1, 77.0, 77.8, 78.3, 79.4, 80.6 (2C), 81.8, 94.9, 98.6, 99.7, 117.7, 118.4, 119.7, 124.9, 135.7, 136.1, 137.6, 140.0, 173.7.	
B1 (0.3 ml. 16%)	
12.0, 12.9, 13.1, 16.4, 17.3, 18.4, 19.9, 20.2, 27.5, 30.6, 34.3 (3C), 35.2, 36.6, 39.8, 40.5, 45.7, 56.4 (2C), 67.3, 67.8, 68.2 (2C), 68.4 (2C), 75.0, 76.1, 78.3, 79.4 (2C), 80.5 (2C), 82.0, 95.0, 95.8, 98.5, 118.1, 118.4, 120.4, 124.8, 127.9, 135.2, 136.2, 137.9 (2C), 139.7, 173.6.	
B2 (0.6 ml. 16%)	
11.8, 12.4, 13.8, 15.1, 17.7, 18.4, 19.9, 20.2, 27.5, 34.4 (3C), 35.2, 35.8, 36.5, 39.8, 40.8, 41.2, 45.8, 56.4 (2C), 67.3, 67.7 (2C), 68.3 (3C), 69.9, 70.9, 76.1, 78.3, 79.4 (2C), 80.5 (2C), 81.8, 94.9, 98.6, 99.7, 117.7, 118.0, 120.4, 124.8, 135.7, 136.0 (2C), 139.8, 173.5.	

The characteristic mass spectral peaks of eight C-076 compounds are given in Table III. The first line of Table III represents the mass to charge ratio (m/e) of the molecular ion of each respective compound, and the remaining numbers record the mass to charge ratio of

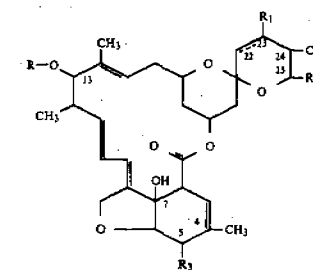
the principal fragments of each compound. Mass to charge ratios found on the same horizontal row indicate analogous fragments in each compound. The mass to charge ratios which are given as whole numbers were obtained from an LKB Mass Spectrometer Model 5 LKB-9000. The mass to charge ratios which are given to the fourth decimal place were obtained from a High Resolution Varian Mass Spectrometer Model MAT-731.

TABLE III

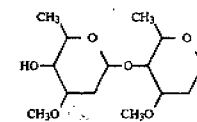
A1a	A1b	A2a	A2b	B1a	B1b	B2a	B2b
886.5072	872	904	890	872	858	890	876
742.4229	728	760	746	728	714	746	732
580.3406	566.3265	598	584	566	552	584	570
548.3136	534	566	552	548.3131	534	566	552
456.2886	442	456	442	456	442	456	442
305.2120	291.1962	323.2225	309.2070	305	291	323	309
		305	291			305	291
275.1292	275	275	275	261.1139	261	261	261
257.1382	257	257	257	257	257	257	257
221.1527	207	238.1637	225	221	207	239	225
193.1587	179.1429	211.1691	197.1542	193	179	211	197
198.1101	199	199	199	199	199	199	199
169.1226	155	179.1076	179	169	155	179	179
145.0667	145	145	145	145	145	145	145
137.0954	137	137	137	137	137	137	137
127.0754	127	127	127	127	127	127	127
113.0604	113	113	113	113	113	113	113
95.0496	95	95	95	95	95	95	95
87.0444	87	87	87	87	87	87	87

The attached FIGS. 1 to 8 are accurate reproductions of infrared and proton-nuclear magnetic resonance spectra of four of the C-076 compounds. FIGS. 1-4 are infrared spectra for C-076 A1a, A2a, B1a and B2a respectively. FIGS. 5 to 8 are proton-nuclear magnetic spectra for C-076 A1a, A2a, B1a and B2a respectively. The infrared spectra were obtained on a Perkin-Elmer Infrared Spectrometer Model 421 in chloroform solution. The proton-nuclear magnetic resonance spectra were obtained in deuterated chloroform solution in a Varian Nuclear Magnetic Resonance Spectrometer Model HA-100 and the spectra show chemical shifts given in parts per million (ppm) relative to tetramethylsilane as an internal standard.

Based on experimental data, including the studies and measurements described herein, the C-076 compounds are believed to have the following planar structural formula:



wherein R is the α-L-oleandrosyl-α-L-oleandroside of the structure:



and wherein the broken line indicates a single or a double bond; R₁ is hydroxy and is present only when said broken line indicates a single bond.

R₂ is iso-propyl or sec-butyl; and
R₃ is methoxy or hydroxy.

In the foregoing structural formula, the individual compounds are as set forth in Table IV.

TABLE IV

	R ₁	R ₂	R ₃
A1a	Double bond	sec-butyl	-OCH ₃
A1b	Double bond	iso-propyl	-OCH ₃
A2a	-OH	sec-butyl	-OCH ₃
A2b	-OH	iso-propyl	-OCH ₃
B1a	Double bond	sec-butyl	-OH
B1b	Double bond	iso-propyl	-OH
B2a	-OH	sec-butyl	-OH
B2b	-OH	iso-propyl	-OH

As might be expected, the compounds of this invention wherein R₂ is butyl (the "a series" of compounds) and the corresponding compound wherein R₂ is propyl (the "b series"), act similarly in most recovery procedures such as those involving solvent extraction. In each pair of "a" and "b" compounds the "a" compound is found in greater amount and generally makes up about 85 to 99% of a mixture of the "a" and "b" compounds. The presence of the iso-propyl compounds is verified in the mass spectra of the compounds wherein the mass peaks representing the fragments containing the butyl group have companion peaks with a mass 14 units (or one-CH₂ group) lower. In addition, high pressure liquid chromatography has been employed to separate the A1b component from the A1a component, and the mass spectrum of such A1b compound has been verified by high resolution mass spectrometry (see Table III).

The novel compounds of this invention have significant parasitocidal activity as anthelmintics, 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 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 C-076 compounds of this invention have unexpectedly high activity against these parasites, and in addition are also active against *Dirofilaria* in dogs, *Nematospiroides*, *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. in 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 parasites 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 gastro-intestinal 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, *Timolea* 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* migratory orthopterus 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. Generally, 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 dicalcium phosphate.

Where it is desired to administer the C-076 compounds 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 C-076 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 the active compound.

Although the antiparasitic agents of this invention find their primary use in the treatment of helminthiasis, they are also useful in the 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 C-076 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% by 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 C-076 compound employed, the compounds of this invention are usually fed at concentrations of between 0.00001 to 0.002% in the feed in order to achieve the desired antiparasitic result.

In using the compounds of this invention, the individual C-076 components may be isolated and purified and used in that form. Alternatively, mixtures more of the individual C-076 components may be used. It is not necessary to completely separate the various C-076 compounds obtained from the purification of the fermentation broth. Generally, there is obtained a mixture containing two or more of the C-076 compounds, but having other unrelated compounds excluded therefrom, and such mixture may be used for the treatment of parasitic diseases as described herein. Such a mixture generally will contain unequal proportions of the C-076 compounds, however, all of the compounds have substantial activity and the antiparasitic activity of the mixture can be accurately determined. In particular it may not be necessary to separate the "b" components from the related "a" component. Such compounds differ only in the length of the 25 side-chain. Separation of these closely related compounds is generally not practiced since the "b" compound is present only in a very small percent by weight.

In addition, where the C-076 compounds are to be added to an animal's feed, it is possible to utilize the dried mycelial cake from the fermentation broth. The mycelia contain a preponderance of the activity and since the level of the activity of the mycelia can be determined, it can be added directly to the animal's feed.

The compounds of this invention have a broad spectrum of activity against many internal parasites at low dosage levels and in many different animals. At levels of about 2.5 mg. per kg. of animal body weight, concentrated mixtures of C-076 compounds are fully active in sheep against *Haemonchus contortus*, *Ostertagia circumcincta*, *Trichostrongylus axei*, *Trichostrongylus colubriformis*, *Cooperia* spp., and *Oesophagostomum columbianum*. Similarly in cattle at dosages as low as 0.043 mg./kg. C-076 B2 is fully active against *Ostertagia ostertagi*, *Trichostrongylus axei*, *Trichostrongylus colubriformis*, *Oesophagostomum radiatum* and *Dictyocaulus viviparus*. In addition, a horse infected with bots (*Gastrophilus intestinalis* and *Gastrophilus haemorrhoidalis*), large and small strongyles and *Oxyuris* was successfully treated with 10 mg./kg. (about 1% active compounds by weight) of a mixed concentrate of C-076 compounds, and a dog infected with the microfilarial stage of heartworm (*Dirofilaria immitis*) was successfully treated with a single oral dose at 10 mg./kg. (about 1% active compounds by weight) of a mixed concentrate of C-076 compounds. In rodents, such as mice, infections of *Syphacia*, *Nematospiroides* and *Aspiculuris* have been successfully treated by the oral administration of the C-076 compounds or of the concentrates obtained from the extraction of the mycelia.

The C-076 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 anthelmintic activity of C-076 may be determined by orally administering via the feed, a sample of C-076 individual compound, a mixture of C-076 compounds, a concentrated extract, and the like to a mouse which had been infected 3 days earlier with *Nematospiroides dubius*. At 11, 12 and 13 days after the initiation of the medication, the feces of the mouse are examined for *N. dubius* eggs, and on the next day the mouse is sacrificed and the number of worms present in the proximal portion of the small intestine are determined. An active compound is observed when there is a significant reduction of egg and worm counts when compared to infected, unmedicated controls.

The following examples are being provided in order that the instant invention may be more fully understood. Such examples are not to be construed as being limitative of the invention.

EXAMPLE 1

The contents of a lyophilized tube of *Streptomyces avermitilis* MA-4680 is transferred aseptically to a 250 ml. Erlenmeyer flask containing 305 ml. of Medium 1. The inoculated flask is incubated for 3 days at 28° C. on a rotary shaking machine at a speed of 220 RPM in a 2 inch radius circular orbit. At the end of this time, a 250 ml. Erlenmeyer flask containing 50 ml. of Medium 2 is inoculated with a 2 ml. sample from the first flask. This flask is incubated for 3 days at 28° C. on a rotary shaking machine at a speed of 220 RPM in a 2 inch diameter circular orbit. 50 ml. of the resulting fermentation broth containing C-076 is effective against an *N. dubius* infection in mice.

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methylene chloride, 10 parts hexane and one part methanol to a final volume of 15 liters. This solution is applied directly to the Sephadex LH-20 column of the next example.

EXAMPLE 11

A 30 centimeter diameter column is prepared in methanol with 36 kilograms of Sephadex LH-20 (available from Pharmacia Fine Chemicals, 800 Centennial Avenue, Piscataway, N.J. 08854) and washed with a solvent consisting of 10 parts methylene chloride, 10 parts hexane and one part methanol. One-fourth of the C-076 solution of Example 10 is applied to the column and the column eluted at a rate of 250 ml. per minute. Two 20 liter forecuts are collected and discarded followed by 20 two liter rich cuts (identified as fractions 1-20), followed by a single 20 liter tail cut, which is discarded. Fractions 1-8 are found to contain the C-076 A compounds and fractions 9-20 are found to contain the C-076 B compounds.

EXAMPLE 12

The process of Example 11 is repeated on the same scale three more times and all of the fractions containing the C-076 B components (fractions 9-20) are combined and evaporated to dryness, affording 818 g. of crude mixed C-076 B components. The sample is found to contain 55% C-076 B1 and 39% of C-076 B2. 680.5 G. of this sample is dissolved in 2 liters of methylene chloride and placed in a 22 liter three neck round bottom flask followed by the addition of 13.6 liters of methanol. The methylene chloride is removed by distillation. 13.6 liters of ethylene glycol is added as the methanol is being distilled under reduced pressure. The rate of distillation is maintained such that the temperature of the solution did not go below 65° C. When the addition of the ethylene glycol is complete, the solution is allowed to cool at 5° C. for sixteen hours. The crystals are filtered and washed with 1 liter of cold ethylene glycol. The crystals are then redissolved in 2 liters of methylene chloride the solution placed in a 22 liter three necked round bottom flask. The procedure described above is repeated twice. The first time 12.5 liters each of methanol and ethylene glycol is employed and the second time 13.6 liters each of methanol and ethylene glycol is employed. The final crystals are washed with 1 liter of cold ethylene glycol and 1 liter of water. The crystals are dissolved in 4 liters of water and dried by filtering through sodium sulfate. The benzene solution is concentrated to a volume of 2 liters and lyophilized affording 241.2 gm. of a white powder consisting of 98% C-076 B1 and 1% of C-076 B2.

The mother liquors (22 liters) from the first two crystallizations above are combined and diluted with 22 liters of water. The aqueous solution is extracted with 60 liters of toluene and again with 15 liters of toluene. The toluene extract is then washed with 48 liters of water. The organic phase is filtered through Super-Cel to remove any residual water and evaporated affording 336 gm. of solid material consisting of 79% C-076 B2 and 16% C-076 B1 compounds.

EXAMPLE 13

In the four Sephadex LH-20 columns of the procedure of Example 11, fractions 1-8 contain the C-076 A compounds and are combined. By HPLC analysis the mixture is found to contain 252 g. of C-076 A2a, 16 g. of A2b, 94 g. of A1a and 24 g. of A1b. The material is

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dissolved in a solvent system consisting of hexane:toluene:methanol in the proportion of 6:1:1 and applied to the Sephadex LH-20 column of the same dimensions as the one used in Example 11 in the above solvent. Fractions are collected at the rate of 250 ml. per minute and a 20 liter forecut is collected and discarded. Further elution affords 2 additional 20 liter forecuts which are also discarded and 50 four liter rich cuts which contain C-076 A compounds. Fractions 1-8 are found to contain predominately C-076 A1 components (46.2 g. A1a and 6.7 g. A1b), and fractions 29-36 are found to contain C-076 A2 compounds (117.2 g. A2a and 7.35 g. of A2b). Fractions 9-28 contain a mixture of C-076 A1 and A2 compounds.

EXAMPLE 14

A sample of 150 g. of C-076 B1 from Example 12 is dissolved in 3 liters of a solvent mixture of hexane:toluene:methanol in the ratio of 3:1:1. The solution is passed through a column of Sephadex LH-20 (of the same dimensions as the one used in Example 11) in the above solvent taking fractions at the rate of 250 ml. per minutes. After two 20 liter portions of the solvent mixture are collected and discarded, forecut of 10 liters is taken and discarded. Then 30 richcuts of 2 liters each are taken. Fractions 1-13 and 25-30 are discarded. Fractions 14-16 are combined and contain 80 g. of predominately C-076 B1a. Fractions 22-24 are combined and contain 6.7 g. of predominately C-076 B1b. Fractions 17-21 contain a mixture of C-076 B1a and B1b.

Fractions 17-21 above are combined and concentrated and passed through a Sephadex LH-20 column with the same solvent system as above. Three 20 liter forecuts are taken and discarded. Richcuts are then taken as follows: 5 cuts of 2 liters each (fractions 1-5); 20 cuts of 1 liter each (fractions 6-25); and 10 cuts of 2 liters each (fractions 26-35). Fractions 1-15 are discarded; fractions 16-21 contain 13.5 g. of C-076 B1a and 0.4 g. of C-076 B1b; fractions 22-28 contain 44 g. of C-076 B1a and 0.13 g. of C-076 B1b; fractions 27-30 contain 10.2 g. of C-076 B1a and 0.8 g. of C-076 B1b.

EXAMPLE 15

A mixture of all 8 C-076 components are chromatographed on a high pressure liquid chromatography column 4 mm. x 30 cm. packed with 10 micron μ Bondapak C₁₈ silica gel (available from Waters Associates Inc., Maple Street, Milford, Massachusetts 01757) eluting with 85:15 (v/v) methanol:water at a constant 40° C. At a flow rate of 1.2 ml. per minute all eight compounds are separated and the elution volumes, which under the foregoing constant conditions are characteristic of the individual compounds are as follows:

	Elution Volume (V _e) ml
C-076 B1b	4.90
C-076 B1a	6.52
C-076 A2b	7.12
C-076 A2a	7.88
C-076 B1b	8.36
C-076 B1a	9.60
C-076 A1b	10.24
C-076 A1a	11.88

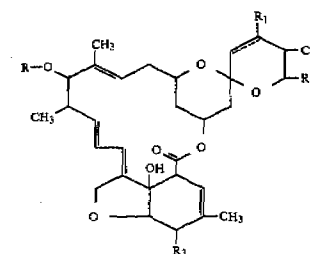
The separation of C-076 "b" components from the respective "a" components is accomplished using techniques such as high pressure liquid chromatography. An absolute methanol solution of 30 microliters of a mix-

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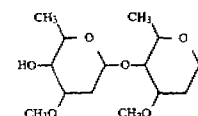
ture of C-076 A1a and A1b, estimated to contain 30 micrograms of C-076 A1b is placed on a 3 x 250 mm. high pressure liquid chromatography column containing Spherisorb 5 micron ODS (available from Spectra Physics) as packing. The column is eluted with 85:15 methanol:water at a rate of 0.15 ml./min. The elution of the products are followed by observing the ultraviolet absorption of the eluent and collecting the individual components at the outlet of the UV monitor. 30 Micrograms of C-076 A1b is recovered and analyzed in a mass spectrometer. The mass spectrum of this sample is recorded in the second column of Table III.

What is claimed is:

1. A compound having the formula:



wherein R is:



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and wherein the broken line indicates a single or a double bond; R₁ is hydroxy and is present only when said broken line indicates a single bond;

R₂ is iso-propyl or sec-butyl; and

R₃ is methoxy or hydroxy.

2. The compound of claim 1 wherein the broken line indicates a double bond, R₂ is iso-propyl and R₃ is methoxy.

3. The compound of claim 1 wherein the broken line indicates a double bond, R₂ is iso-propyl and R₃ is hydroxy.

4. The compound of claim 1 wherein the broken line indicates a double bond, R₂ is sec-butyl and R₃ is methoxy.

5. The compound of claim 1 wherein the broken line indicates a double bond, R₂ is sec-butyl and R₃ is hydroxy.

6. The compound of claim 1 wherein the broken line indicates a single bond, R₁ is hydroxy, R₂ is iso-propyl and R₃ is methoxy.

7. The compound of claim 1 wherein the broken line indicates a single bond, R₁ is hydroxy, R₂ is iso-propyl and R₃ is hydroxy.

8. The compound of claim 1 wherein the broken line indicates a single bond, R₁ is hydroxy, R₂ is sec-butyl and R₃ is methoxy.

9. The compound of claim 1 wherein the broken line indicates a single bond, R₁ is hydroxy, R₂ is sec-butyl and R₃ is hydroxy.

10. A composition useful for the treatment of parasitic diseases which comprises an inert carrier having a pharmaceutically effective amount of one or more of the compounds of claim 1 incorporated therein.

11. The composition of claim 10 which is a solid or liquid unit dosage formulation containing from 0.001 to 0.5% by weight of the active compound.

12. The composition of claim 10 which is a feed supplement containing from 0.0002 to 0.3% by weight of the active compound.

13. The composition of claim 10 which is a feed premix containing from 0.005 to 2.0% by weight of the active compound.

14. The composition of claim 10 which is a parenteral formulation containing from 0.005 to 0.5% by weight of the active compound.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

202075
Bogotá, D.C.,

Abogado
MARGARITA CASTELLANOS ABONDANO.

ASUNTO	Radicación	05059203
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	
	Folios	013

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐
		Cap. II	☒

No. Sol. Internacional	PCT/EP2003/014613
Fecha de Presentación Internal.	19-12-2003.

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:

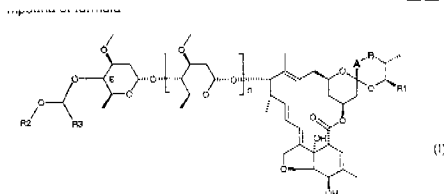
Documentos estudiados

<u>Descripción:</u>	Folios: 91 a 174 (como se radicó inicialmente)
<u>Reivindicaciones:</u>	Folios: 175 a 179 (como se radicó inicialmente)
<u>Prioridad:</u>	Folio 1 (20-12-2002, GB 0229804.0).

Objeto de la invención

Título de la solicitud: Avermectina B1 y derivados de monosacáridos de avermectina B1 que tienen un sustituyente alcóximetilo en la posición 4 'o 4'

El objeto de la presente solicitud de patente de invención consiste en:
Compuestos derivados de Avermectina B1



Reivindicación 1-5: Un compuesto de fórmula I.

Reivindicación 6: Un pesticida que lo contiene

Reivindicación 7 : Un método para controlar plagas.

El problema planteado en esta solicitud es la necesidad proporcionar compuestos que tienen propiedades pesticidas especialmente en el control de insectos y miembros del orden de la acarina.

Para solucionar este problema técnico la solicitud en estudio proporciona los compuestos derivados de avermectina de fórmula I.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la Clasificación Internacional de Patentes (IPC): C07H17/08, A61K31/70, A61P33/00

De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

La no son concisas por las siguientes razones:

- Existen múltiples posibilidades de sustitución a nivel del compuesto de fórmula I para los radicales R₂-R₃ especificados de acuerdo con los parámetros de sustitución señalados.
- Para las reivindicaciones 1-4 se encuentran términos como: **Arilo, heterocíclico, ariloxi, ariltio, heterocicililoxi, aril-alquilo C₁-C₁₂ heterocicilil-alquilo C₁-C₁₂** ya que no se especifica el número de carbonos que los conforman, no se define su tamaño y adicionalmente en el caso de heterocíclico no se especifica el número y clase de heteroátomos que lo conforman y si es saturado o no.

Se le requiere al interesado en lo posible definir los términos como por ejemplo en el caso de arilo (fenilo, naftilo etc...), si es heterocíclico (morfolino, piperidina etc..) y que se encuentren debidamente sustentados en la descripción.

Claridad

- En la reivindicación 1 en el folio 178 en las excepciones se habla de n=2 pero según la definición de n en el folio 175 n=2 no está dentro del alcance de los compuestos de fórmula (I). En las mismas excepciones se habla de compuestos de avermectina B₂, pero la fórmula I no está de acuerdo con este tipo de compuestos ya que según la definición en la página 4 de la descripción los compuestos B₂ tienen un grupo 23-OH (sustituyente en -A-B)

Excepción a la patentabilidad (artículo 20 D486 literal a)-d))

Se aclara que, de acuerdo al Art 20 literal d) el método para controlar plagas de la reivindicación 7, no es patentable

Determinación del Estado de la Técnica

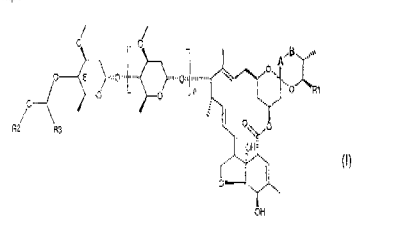
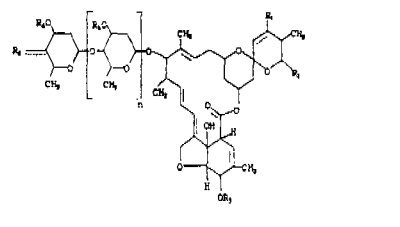
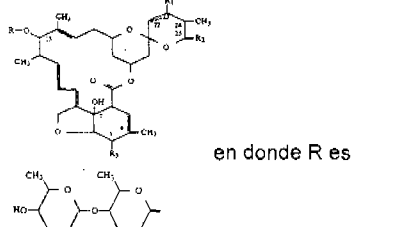
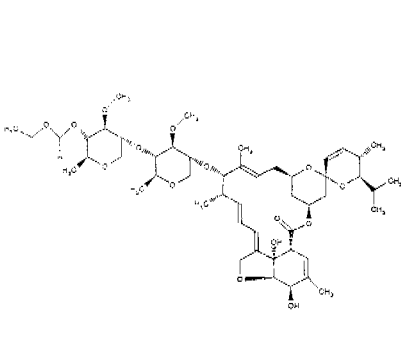
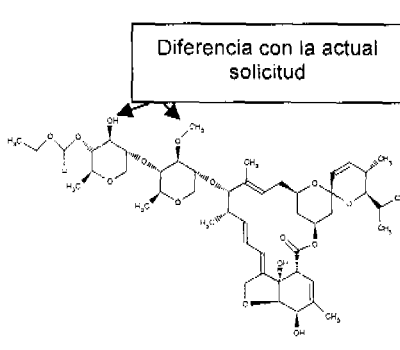
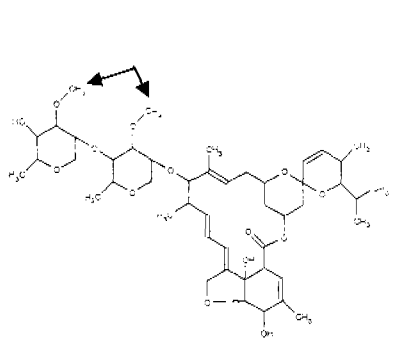
Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 20-12-2002, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Nº	Documento	Título	Fecha de Publicación*
D1	US5169839	DERIVATIVES OF 3'- AND 3"-O-DESMETHYL AVERMECTIN COMPOUNDS, COMPOSITIONS AND METHODS OF TREATING MELMINTIC AND PARASITIC INFECTIONS	8-12-1992
D2	US4310519	NOVEL SUBSTANCES AND PROCESS FOR THEIR PRODUCTION	12-01-1982

Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (artículo 18 D486)

Para la reivindicación 1 en donde se reclama : Un compuesto de fórmula I .

SOLICITUD	D1 US5169839	D2 US4310519
		 en donde R es
En donde	En donde	En donde
R1 es alquilo C ₁ -C ₁₂ (secbutilo) o isopropilo.	R2 es alquilo ramificado C ₃ -C ₈	R2 es secbutil o isopropil
A-B es -CH=CH-	Existe el doble enlace sobre R1 Y R1 es hidrógeno	Existe el doble enlace sobre R1 y R1 es hidrógeno
R2 es alquilo C ₁ -C ₁₂ (CH ₂ CH ₃) R3 es hidrogeno.	R6 es alcoxibajometoxi. (etoximetoxi).	
n es 1	n es 1	
	R3 es hidrógeno	R3 es hidroxi
Ambos radicales son metilo	R4 y R5 no son simultáneamente metilo.	Ambos radicales son metilo.
 Compuesto 1.5 Tabla 1	 Diferencia con la actual solicitud	

El documento del estado de la técnica más cercano es D1 (Folios 219-222) que divulga compuestos derivados de avermectina caracterizados por tener actividad como agentes antiparasitarios.

La solicitud se diferencia de D1 en que los radicales equivalentes a R4 y R5 en D1 son simultáneamente metilo .

Esta diferencia no parece conceder un efecto técnico inesperado ò una ventaja a las compuestos reclamados en esta solicitud ya que no parecen presentar un mayor actividad antiparasitaria en comparación con los compuestos del estado de la técnica más cercano.

El Problema Técnico Objetivo de esta solicitud es la necesidad de compuestos caracterizados por ser agentes antiparasitarios alternativos a los ya conocidos en el estado del arte.

D2 (Folios 223-226), enseña compuestos derivados de avermectina en los cuales los radicales equivalentes a R4 y R5 en D1 son simultáneamente grupos metilo y se caracterizan por tener actividad antiparasitaria

El Experto en la Materia, enfrentado al Problema Técnico Objetivo y conociendo el Estado de la Técnica (D1 y D2) hubiera sugerido sin mucho esfuerzo de su parte sustituir por grupos metilo los radicales R4 y R5 de D1 de manera simultanea de acuerdo a las enseñanzas de D2 para obtener más compuestos con la misma actividad .

De manera que la solución propuesta por esta solicitud en las reivindicaciones 1-5 es obvia y no tiene Nivel Inventivo.

El pesticida de la reivindicación 6 no tiene nivel inventivo porque el compuesto que lo caracteriza no es inventivo.

Conclusión:

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

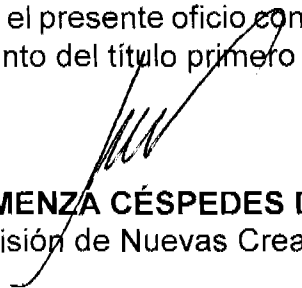
N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	US5169839	1-6	Nivel inventivo.
D2	US4310519	1-6	Nivel inventivo.

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.

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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 División de Nuevas Creaciones

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

CONCEPTO TÉCNICO No. 2309	EXAMINADOR TÉCNICO Código No. 202075
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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

202075

Bogotá, D.C.

DOCTOR(A) : **MARGARITA CASTELLANOS ABONDANO.**

ASUNTO :

Radicación N°	05059203
Trámite	002
Evento	001
Actuación	430
Oficio	
Folios	002

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 46 de la decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

Solicitud de documentos, según artículo 46.

De acuerdo con el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina se requiere del solicitante la presentación de los artículos :

1. **TSUKAMOTO, YOSHIHISA ET AL: "Avermectin chemistry and action: ester- and ether-type candidate photoaffinity probes" BIOORGANIC & MEDICINAL CHEMISTRY (2000), 8(1), 19-26 , 2000, XP002280644.**
2. **SHOOP, W. L. ET AL: "Efficacy in sheep and pharmacokinetics in cattle that led to the selectio of eprinomectin as a topical endectocide for cattle" INTERNATIONAL JOURNAL FOR PARASITOLOGY (1996), 26(11), 1227-1235 , 1996, XP002280645.**
3. **JONES, TODD K. ET AL: "Synthesis and Biological Activity of 4a,4"- Disubstituted Avermectins" JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY (1994), 42(8), 1786-90 , 1994, XP002280646**

En cumplimiento del artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe proporcionar éstos documentos, en un plazo que no excederá de tres (3) meses, a partir a partir de la fecha de la notificación de la presente comunicación. Si el solicitante no presentara los documentos requeridos dentro del plazo señalado, la oficina nacional competente denegará la patente.

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Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la circular única N° 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 _____

CONCEPTO TÉCNICO: No. 2466	EXAMINADOR TÉCNICO Código 202075
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