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CAVELIER

ABOGADOS

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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EDIFICIO SISKI
CARRERA 4 No. 72 - 3º
BOGOTÁ 8, COLOMBIA



No. 06-098507- -00002-0000

Fecha: 2007-09-25 16:42:15 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 8

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

Trámite : 011
Evento : 378
Actuación : 538

Referencia : Expediente No. 06.098.507
Asunto : Solicitud de Patente para **1,3,4-OXADIAZOL-2-ONAS
COMO MODULADORES DEL PPAR DELTA Y LOS
USOS DE LAS MISMAS.**

Solicitante : **AVENTIS PHARMACEUTICALS, INC.**
Clase : A61K 031/4245, C07D 271/000
Publicada en : La Gaceta No. 574 Del 30 de marzo de 2007
Fecha de Solicitud : 29 de septiembre de 2006

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capítulo I del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo por valor de \$404.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 36155 de 28 de diciembre de 2006.

2. Presento junto con este escrito el documento de poder otorgado por la compañía **AVENTIS PHARMACEUTICALS, INC.**, con el fin de continuar y llevar hasta su culminación el trámite de administrativo de la patente de la referencia.

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

Señora Jefe,

EMILIO FERRERO
T.P.A. No. 31.929

2013 COLO 15896 841 006 4
FBH\ASG\ID-107204\WPC15896
No. M-2007-107204\FBH

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-098507- -00002-0000

Fecha: 2007-09-25 16:42:15 Dep. 2020 NUECREACIONE
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 61,629
FECHA : JULIO 31 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	63769915	31/07/2007	55,200,000.00

***** CONCEPTO *****

CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	
85 EXAMEN DE PATENTABILIDAD DE INVEN	404,000.00
TOTAL :	\$ 404,000.00

SON: CUATROCIENTOS CUATRO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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APOSTILLE

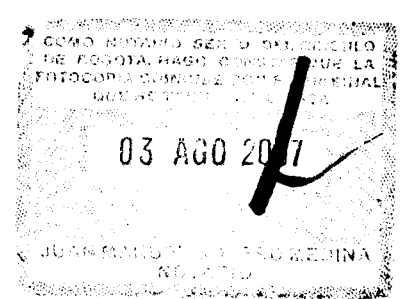
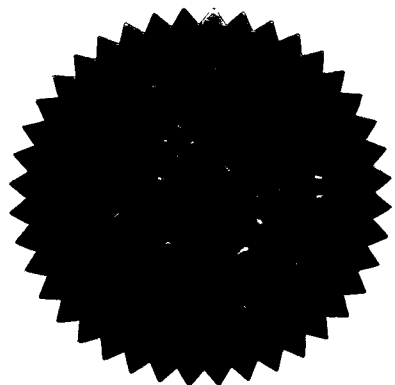
(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

- 1. COUNTRY: UNITED STATES OF AMERICA
- 2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
TINA M WISBESKI
- 3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
- 4. BEARS THE SEAL/STAMP OF:
TINA M WISBESKI, NOTARY

CERTIFIED

- 5. AT TRENTON, NEW JERSEY
- 6. THE 5TH DAY OF MARCH 2007
- 7. BY: Bradley Abelow, NEW JERSEY TREASURER
- 8. NO. A284990
- 9. SEAL/STAMP:
- 10. SIGNATURE

Bradley Abelow



Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.

Representation and Power-of-Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION Y PODER

REPRESENTATION AND POWER-OF-ATTORNEY

Yo (nosotros), abajo firmado (s)/I (we), the undersigned

AVENTIS PHARMACEUTICALS INC

domiciliado (s) en/of 300 Somerset Corporate Boulevard
Bridgewater, New Jersey 08807
United States of America

por el presente nombramos a EMILIO FERRERO, tpa. 31929; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y DANIEL PEÑA, tpa. 65.620, domiciliados en la Carrera 4a N° 72-35, Bogotá, Colombia, en obediencia a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso. Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and DANIEL PEÑA, tpa. 65620, domiciled at Carrera 4a N° 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time. In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition,

consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

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protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

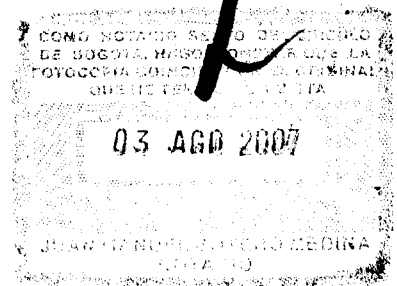
Dado y firmado hoy/Given and signed this 27 Day of February 2007

en/in Bridgewater, New Jersey United States of America

por/by Andrea Q. Ryan, Assistant Secretary

Firma/Signature

Andrea Q. Ryan



NOTARIAL CERTIFICATE
(Corporation)

UNITED STATES OF AMERICA)
STATE OF NEW JERSEY) ss.
COUNTY OF SOMERSET)

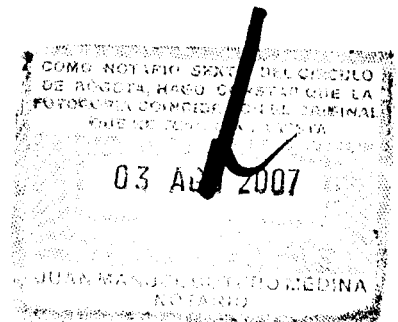
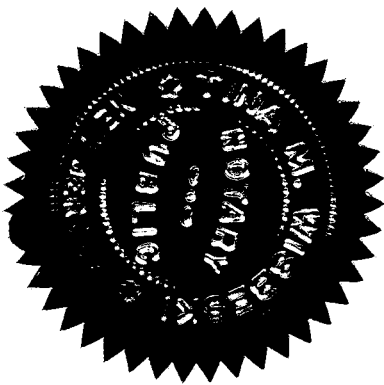
On this 27th day of February, 2007, personally appeared before me, **Andrea Q. Ryan**, Assistant Secretary, known or identified to me to be the individual described in and who executed the foregoing document, **Power of Attorney**, and acknowledged the same as a free act and deed for uses and purposes therein expressed by authority of the said Corporation incorporated under the laws of the State of Delaware, United States of America.

I further certify that said authority, dated **December 19, 2003**, is based on a **Resolution of the Board of Directors of said Corporation**, which I have seen, appointing the said individual Assistant Secretary with full power to sign the foregoing document on behalf of the said Corporation and that the purposes for which said document is granted are within the scope of the objects or activities of said Corporation,

SEAL


Notary Public

Tina M. Wisbeski
Notary Public, State of New Jersey
My Commission Expires August 5, 2009



TRADUCCIÓN OFICIAL 115/2007 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL DE ACUERDO CON EL CUAL **AVENTIS PHARMACEUTICALS INC**, EMPRESA DOMICILIADA EN 300 SOMERSET CORPORATE BOULEVARD, BRIDGEWATER, NEW JERSEY 08807, ESTADOS UNIDOS DE AMÉRICA OTORGA PODER A EMILIO FERRERO, TPA 31929; LUZ CLEMENCIA DE PAEZ, TPA 23555 Y A DANIEL PEÑA, TPA 65620.

EXPEDIDO Y FIRMADO HOY 27 DE FEBRERO DE 2007 EN BRIDGEWATER, NEW JERSEY, ESTADOS UNIDOS DE AMÉRICA, POR ANDREA Q. RYAN, APODERADO

FIRMADO: (ILEGIBLE)

CERTIFICACIÓN NOTARIAL

(SOCIEDAD)

ESTADOS UNIDOS DE AMÉRICA

ESTADO DE NUEVA JERSEY

CONDADO DE SOMERSET

DECLARACIÓN JURADA

Hoy 27 de febrero de 2007, compareció personalmente ante mí, ANDREA Q. RYAN, apoderado, conocido o quien se identificó ante mí como la persona descrita y quien firmó el documento precedente, poder, y reconoció el mismo como un acto de su libre albedrío para los usos y objetivos allí expresados, mediante autorización de dicha sociedad, constituida de acuerdo con las leyes del estado de Delaware, Estados Unidos de América.

Además certifico que dicha autorización, de fecha 19 de diciembre de 2003, se basa en la resolución de la junta directiva de dicha resolución, que he visto, y designó a dicho secretario asistente con plenos poderes para firmar el documento precedente a nombre de dicha empresa y que los objetivos para los cuales se otorga dicho documento

03 AGO 2007

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están dentro del alcance del objeto social o actividades de dicha sociedad.

FIRMADO: TINA M. WISBESKI.

SELLO: NOTARIO PÚBLICO, ESTADO DE NUEVA JERSEY, MI CARGO VENCE EL DE AGOSTO DE 2009.

APOSTILLA

(CONVENCIÓN DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. PAIS: ESTADOS UNIDOS DE AMÉRICA

Este documento público

2. ha sido firmado por TINA M WISBESKI

3. quien actúa en su calidad de NOTARIO PÚBLICO DE NUEVA JERSEY

4. y lleva el sello/estampilla de TINA M. WISBESKI, NOTARIO

CERTIFICADO

5. en Trenton, Nueva Jersey 6. el 5 de marzo de 2007

7. por: Bradley Abelow, tesorero de Nueva Jersey

8. Certificado número A284990

9. Sello: (ILEGIBLE)

10. Firma: BRADLEY ABELAI

COLO- 15896-841-006-4

WPCL002G ID 8837

Bogotá, 16 de mayo de 2007.

Eduardo Calado
Eduardo Calado Rosales
TRADUCTOR OFICIAL
INGLES - ESPAÑOL - INGLES
Res. 341 Febrero de 1976

COMO NOTARIO SELECCIONADO POR EL GOBIERNO DE BOGOTÁ, HAGO CONSTAR QUE LA FOTOCOPIA CUMPLE CON LOS REQUISITOS QUE SE LE PEDIEN.
03 AGO 2007

852919
Eduardo Calado
Cuya firma aparece en el
documento reseña
las funciones indicadas

8529.19

Edwino Ceballos

CUYA FIRMA APARECE EN EL

DOCUMENTO DESEMPEÑO

LAS FUNCIONES INDICADAS

03 AGG 2007

2007 MAY 17 P 12: 15

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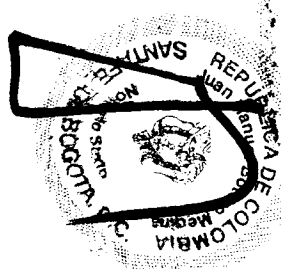
JEFE DE LEGALIZACIONES

BOGOTA D.C.

COINCIDE(N) CON LA FIRMA REGISTRADA POR
EL (ELLOS) EN ESTA NOTARIA
SANTAFE DE BOGOTA. 17 MAY 2007

COMO NOTARIO SEXTO DE CIRCULO DE BOGOTA, HAGO CONSTAR QUE EL(A) SR(A) [REDACTED]

ARIO SEXTO DE CIRCULO DE
HAGO CONSTAN QUE LAS
Venerables Señores
Damas de la
Comunidad de la
Calle de la
Calle de la
Calle de la



DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-98507

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **574** DE

FECHA **30 DE MARZO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **03 DE JULIO 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



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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/42, C07D 263/30	A1	(11) International Publication Number: WO 96/13264 (43) International Publication Date: 9 May 1996 (09.05.96)
(21) International Application Number: PCT/US95/14100 (22) International Filing Date: 31 October 1995 (31.10.95) (30) Priority Data: 08/332,667 1 November 1994 (01.11.94) US (60) Parent Application or Grant (63) Related by Continuation US 08/332,667 (CON) Filed on 1 November 1994 (01.11.94) (71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DOMINIANNI, Samuel, James [US/US]; 6010 East 56th Street, Indianapolis, IN 46226 (US). FITCH, Lora, Louise [US/US]; 5720 Susan Drive, East, Indianapolis, IN 46250 (US). SCHMIEGEL, Klaus, Kurt [US/US]; 4507 Staughton Drive, Indianapolis, IN 46226 (US).	(74) Agent: LAMMERT, Steven, R.; Barnes & Thornburg, 1313 Merchants Bank Building, 11 South Meridian Street, Indianapolis, IN 46204 (US). (81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG). Published <i>With international search report.</i>	
(54) Title: ORAL HYPOGLYCEMIC AGENTS (57) Abstract Antihyperglycemic compounds selected from the group consisting of C-substituted pentacycloazoles and N-alkyl-substituted pentacycloazoles.		

-1-

TitleORAL HYPOGLYCEMIC AGENTS5 Background of the Invention

This invention relates to C-substituted pentacycloazoles containing heteroatoms in the 2, 3 and 5 positions of the pentacycloazole ring and N-substituted pentacycloazoles containing nitrogen atoms in either the 2 and 4 positions or in the 3 position of the pentacycloazole ring.

Ellingboe et al. state in the J. Med. Chem., Vol. 36, pages 2485-2493 (1993), which is hereby incorporated by reference, that drugs currently available for the control of the hyperglycemia associated with type 2 (non-insulin dependent) diabetes mellitus possess significant liabilities or efficacy limitations and that considerable effort has been directed toward the development of novel, orally active antihyperglycemic drugs. They also state that many of these new compounds incorporate a relatively acidic heterocycle which serves as the pharmacophore responsible for antihyperglycemic activity, such as thiazolidine-2,4-dione, tetrazole and oxazolidine-2,4-dione rings. In an earlier paper, J. Med. Chem. Vol. 35, pages 1176-1183 (1992), which is hereby incorporated by reference, Ellingboe et al.

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described a number of antihyperglycemic agents, which contain an acidic 3H-1,2,3,5-oxathiadiazole 2-oxide ring, appended via a methylene bridge to numerous aromatic systems. Kangi et al. E.P. 177, 353, which is hereby incorporated by reference, disclose antihyperglycemic thiazolidine pharmacophore
5 appended via a methylene bridge to suitable aromatic systems.

The general object of this invention is to provide new antihyperglycemic compounds based on new pharmacophores. Other objects appear hereinafter.

10 In one aspect, this invention is an antihyperglycemic compound selected from the group consisting C-substituted pentacycloazole pharmacophore containing heteroatoms in the 2,3 and 5 position of the pentacycloazole ring and N-substituted pentacycloazole pharmacophore
15 containing nitrogen atoms in a position selected from the group consisting of the 2 and 4 positions of the pentacycloazole ring and the 3 position of the pentacycloazole ring.

In a second aspect, this invention is an
20 antihyperglycemic composition comprising a pharmaceutically acceptable carrier, diluent or excipient and an effective amount of an antihyperglycemic compound selected from the group consisting C-substituted pentacycloazole pharmacophore containing heteroatoms in the 2,3 and 5 position of the
25 pentacycloazole ring and N-alkyl substituted pentacycloazole pharmacophore containing nitrogen or other hetero atoms in a position selected from the group consisting of the 2 and 4 positions of the pentacycloazole ring and the 3 position of the pentacycloazole ring.

30 In a third aspect, this invention is a method of reducing the hyperglycemia associated with non-insulin dependent diabetes mellitus which method comprises orally administering to a mammal, such as a human, a therapeutic

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dose of an antihyperglycemic compound selected from the group consisting C-substituted pentacycloazole pharmacophore containing heteroatoms in the 2, 3 and 5 position of the pentacycloazole ring and N-substituted pentacycloazole pharmacophore containing nitrogen atoms in a position selected from the group consisting of the 2 and 4 positions of the pentacycloazole ring and the 3 position of the pentacycloazole ring.

We have now found that the objects of this invention can be attained with antihyperglycemic compounds having a C-substituted pentacycloazole pharmacophore containing heteroatoms in the 2, 3 and 5 position of the pentacycloazole ring or an N-alkyl-substituted pentacycloazole pharmacophore (where the alkyl group has 1 to 12 carbon atoms) containing nitrogen atoms in both the 2 and 4 positions or in the 3 position of the pentacycloazole ring wherein the pentacycloazole ring is linked to a suitable aromatic system utilized with pharmacophores responsible for antihyperglycemic activity by an aliphatic group of 1 to 2 carbon atoms and a carbon atom of said aliphatic group is bonded directly to the pentacycloazole ring. Our studies have shown that other things being equal, many other compounds containing different pentacycloazole moieties, lack the antihyperglycemic activity of the compounds of this invention. Further, it appears that if the pentacycloazole moiety is linked to the same aromatic system by an isomeric aliphatic group having no carbon atom bonded to the pentacycloazole ring, the compound lacks antihyperglycemic activity. For example, when a -CH₂-S- linker was employed, the compound was inactive when the "S-" part of the linker was bonded to a C-pentacycloazole moiety and active when the "CH₂-" part of the linker was bonded to a C-pentacycloazole moiety. Likewise, when the pharmacophore was bonded directly

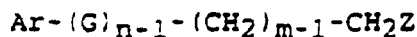
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to the aromatic moiety without an aliphatic linking group, the compounds were inactive.

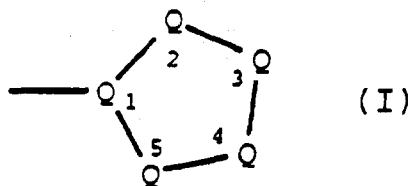
- While Mullican et al. in the J. Med. Chem., Vol. 36, pages 1090-1099 (1993) disclose a C-substituted-
5 2,3,5-triazole linked through methylene to a 4-hydroxy-3,5-dibutylphenyl moiety at page 1091 and Boschelli et al. in J. Med. Chem., Vol. 36, pages 1802 to 1810 (1993) disclose a C-substituted pentacycloazole containing heteroatoms in the 2,3 and 5 position linked through methylene to a
10 dichlorophenylaminophenyl group moiety at page 1804, neither article describes or suggests that the compounds have antihyperglycemic activity. Further, to the best of our knowledge neither the 4-hydroxy-3,5-dibutylphenyl moiety nor the dichlorophenylaminophenyl group have been used with
15 pharmacophores responsible for antihyperglycemic activity.

The compounds of this invention can be represented by the structure



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The bond of attachment to Z is assigned number 1 as described in the following schematic structure formula (I):



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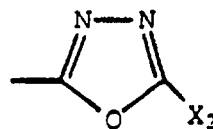
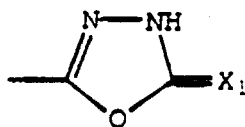
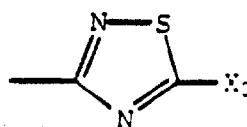
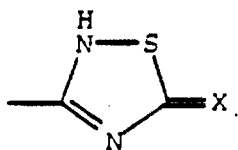
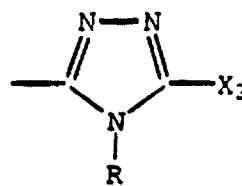
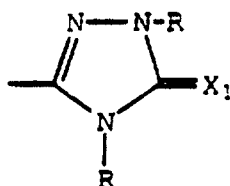
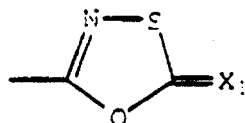
where each Q is independently C, N, O, or S as described in the following definition of Z.

157

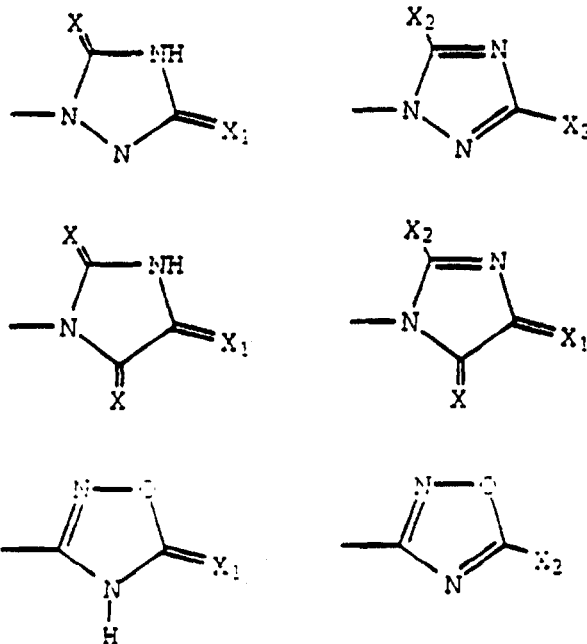
-5-

Z is a C-substituted pentacycloazole containing heteroatoms in the 2, 3 and 5 positions of the pentacycloazole ring or an N-substituted (N at position 1) pentacycloazole containing N atoms in either the 2 and 4 positions or in the 3 position of the pentacycloazole ring; G is oxygen or sulfur; m and n are whole numbers ranging from 1 to 2; and Ar is a suitable aromatic system.

In somewhat greater detail, Z can have any of the structures inclusive of double bond tautomeric forms as follows:



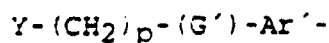
-6-



wherein X_1 is O or S; X_2 is -SR; and each R is independently selected from H, methyl, ethyl, propyl and butyl.

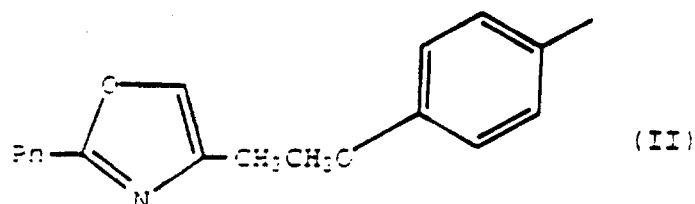
- 5 Ar can be any suitable aromatic system utilized with other pharmacophores responsible for antihyperglycemic activity such as those disclosed in the aforesaid Ellingboe et al. articles; the aforesaid Kangi et al. E.P. 177, 353; Momose et al. in Chem. Pharm. Bull., Vol. 39, No. 6 at pages
 10 1440 to 1445 (1991); Cantello et al. E.P. 415605; Clark et al. U.S. 4,791,125; Kees U.S. 5,183,825; Goldstein et al. WO 93/00343; Hindley E.P. 306,228 all of which are hereby incorporated by reference. Accordingly, the aromatic systems can range from simple dihydronaphthalene moieties in U.S.
 15 5,183,825 to aromatic rings linked to heterocyclic rings.

The preferred aromatic systems can be represented by the structure:



-7-

wherein Ar' is a divalent arylene moiety, such as phenylene, methyl substituted phenylene, chlorophenylene, etc.; G' is O or S; and Y is a cycloalkyl ring, such as methylcyclohexyl, a substituted or unsubstituted aryl group or a heterocyclic
5 such as 2-phenyl-4-oxazolyl; p is a number from 1 to 6. An illustrative Ar' group is shown in formula (II):



10

As is demonstrated in the Examples, the various C-substituted pentacycloazole compounds of this invention can be prepared by routine techniques. For example, C-substituted 2,3,5-triazoles can be prepared by reacting

15

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-9-

A C-substituted 2,5-diazole can be prepared by reacting $\text{ArCH}_2\text{CN} + \text{CH}_3\text{OH} + \text{HCl}$ to form $\text{ArC}(=\text{NH}_2)\text{OCH}_3^+\text{Cl}^-$ followed by Na in CH_3OH to form an amidoxime and then treating with carbonyldiimidazole.

- 5 A C-substituted-1,3,4-oxathiazolin-5-one can be prepared by converting



- 10 to the amide followed by cyclization with chlorocarbonylsulfonyl chloride.

- A C-substituted 1,2,4-thiadiazolin-5-one can be prepared by reacting $\text{ArC}(=\text{NH}_2)\text{OCH}_3^+\text{Cl}^-$ described above with sodium hydride and cyclizing with chlorocarbonylsulfonyl chloride.
- 15

A N-substituted azole can be prepared either by reaction route (1) or (2) below:

- (1) Reacting ArCHO with semicarbazide hydrochloride followed by reduction with boron hydride and cyclizing with carbonyldiimidazole or;
- 20
- (2) Reacting ArCH_2NH_2 with sodium cyanate and cyclizing with diethyl oxylate.

- 25 The compounds of this invention and salts thereof exhibit excellent blood-glucose and blood-lipid lowering actions in mammals (e.g., mouse, rat, dog, cat, monkey, horse, and human beings), and show a low degree of toxicity in terms of both acute and subacute toxicities. Therefore,
- 30 the compounds and salts thereof are of value to human beings

-10-

for the treatment of hyperlipemia, diabetes and their complications.

The compounds of this invention are generally compounded with "pharmaceutically acceptable" carriers, diluents or excipients, which are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The specific dose of a compound administered according to this invention to obtain therapeutic or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the compound administered, the route of administration and the condition being treated. Typical daily doses will contain a non-toxic dosage level of from about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound of this invention. Preferably the pharmaceutical formulation is in unit dosage form. The unit dosage form can be a capsule or tablet itself, or the appropriate number of any of these. The quantity of active ingredient in a unit dose of composition may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. The compound can be administered by a variety of routes although oral is greatly preferred.

Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) a therapeutically effective amount of the compounds of the invention together with a pharmaceutically acceptable carrier or diluent therefor. In making the compositions of the present invention, the active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a

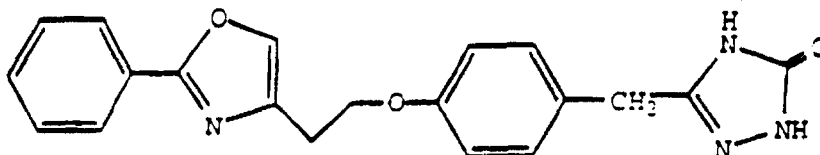
-36-

Example 12

Preparation of:

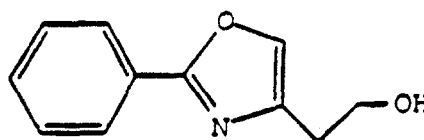
5-[(4-(2-(2-Phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-triazolin-3-one.

5

Part 2

Preparation of:

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To an ice-cooled suspension of 5.87 g (0.155 mol) of LiAlH_4 in 700 mL of Et_2O was added a solution of 35.53 g (0.154 mol) of ethyl 2-phenyl-4-oxazoleacetate in 300 mL of Et_2O over a 1.5 hour period. The temperature of the reaction during the addition was kept below 15°C . After stirring for 2 hours at 25°C the reaction was decomposed by the addition of 15 mL of EtOAc and 33.5 mL of H_2O . The mixture was filtered through anhydrous Na_2SO_4 and concentrated in vacuo to leave 28.1 g of oil. Distillation of the crude oil gave 2-(2-phenyl-4-oxazolyl)ethanol (23.52 g, 81%, bp $120-122^\circ\text{C}/0.05-0.06\text{ mm}$) as an oil which solidified on standing. Elemental analysis for $\text{C}_{11}\text{H}_{11}\text{NO}_2$, Calcd.: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.78; H, 5.90; N, 7.49.

-39-

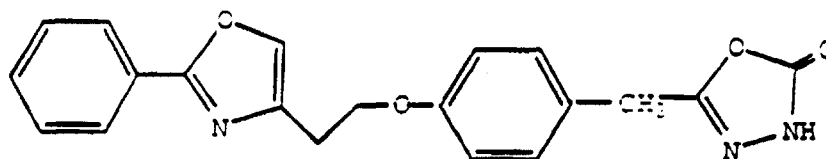
Elemental analysis for $C_{20}H_{18}N_4O_3$, Calcd.:

C, 66.29; H, 5.01; N, 15.46. Found: C, 66.14; H, 5.11; N, 15.41. FD-MS m/e 362; NMR (DMSO- d_6): δ 3.944 (t, 2H), 3.585 (s, 2H), 4.195 (t, 2H), 6.870 (d, 2H), 7.113 (d, 2H), 7.464-7.482 (m, 3H), 7.898 - 7.928 (m, 2H), 7.983 (s, 1H), 11.104 (s, 1H), 11.198 (s, 1H).

Example 13

Preparation of:

5-[(4-(2-(2-Phenyl-4-oxazolyl)ethoxy)phenyl)methyl]2,3,4-oxadiazolin-3-one.



15 A solution of 1.4 mL of phenyl chloroformate in 20 mL of CH_2Cl_2 was added to a stirred mixture of 3.45 g of hydrazide from Example 1 Part B, 1.5 mL of Py and 800 mL of CH_2Cl_2 at 15°C. After stirring for two days at 25°C, 630 mL of solvent was removed and the mixture was stirred for
20 another five days. Methylene chloride was added to bring the total volume to 500 mL and the reaction was washed successively with aqueous $NaHCO_3$, aqueous 5% citric acid, H_2O and dried over anhydrous Na_2SO_4 . Evaporation of the solvent after filtration left 4.9 g of residue which was
25 chromatographed on 120 g of silica. Elution with 1-2% MeOH in CH_2Cl_2 gave 1.9 g of a mixture of intermediate phenoxycarbonyl hydrazide and product 1,3,4-oxadiazol-3-one. Further elution with 3% MeOH in CH_2Cl_2 provided 1.3 g of recovered starting hydrazide.

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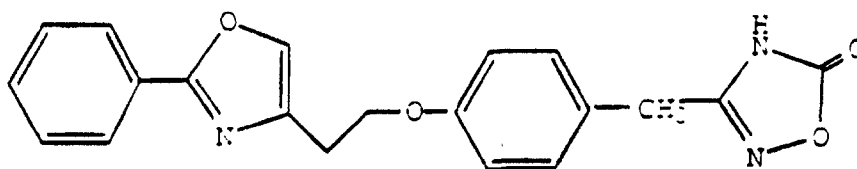
The 1.9 g of the above mixture was dissolved in 175 mL of EtOH and treated with 30 ml of 1N NaOH for 2.5 hours at 25°C. After acidification with aqueous HCl, the solvent was removed and the residue was dissolved in CHCl₃, washed with H₂O and brine and dried over anhydrous Na₂SO₄. Removal of the solvent left 2.0 g of white solid which was recrystallized from 50 mL of MeOH to give 1.3 g of 5-[(4-(2-(2-phenyl-4-oxazolyl)-ethoxy)phenyl)methyl]1,3,4-oxadiazolin-2-one (56%, mp 142-144°C).

Elemental analysis for C₂₀H₁₇N₃O₄, Calcd.: C, 66.11, H, 4.72, N, 11.56. Found: C, 65.84, H, 4.90, N, 11.34. FD-MS: m/e 363; NMR (DMSO-d₆): delta (t, 2H), 3.799 (s, 2H), 4.209 (t, 3H), 6.903 (d, 2H), 7.155 (d, 2H), 7.463-7.483 (m, 3H), 7.905 - 7.931 (m, 2H), 7.988 (s, 1H), 12.072 (br.s, 1H).

Example 14

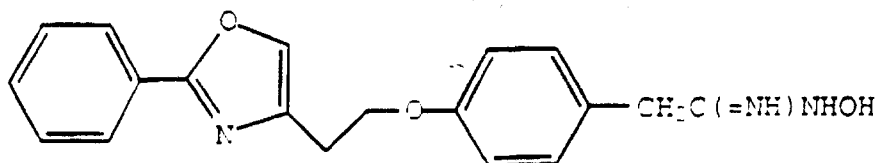
Preparation of:

3-[(4-(2-(2-Phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-oxadiazolin-5-one.



Part A

Preparation of:



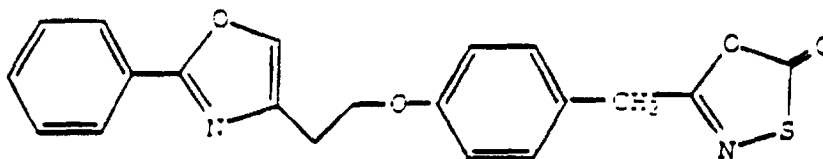
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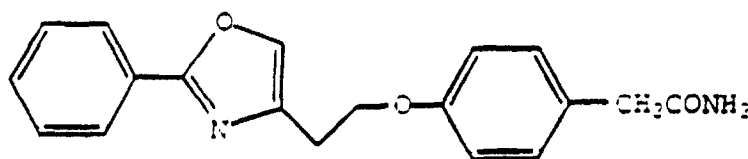
Example 15

Preparation of:

5-[(4-(2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,3,4-oxathiazolin-2-one

Part B

10 Preparation of:



A solution of 0.5 g of methyl ester of Example 1 Part A, 50 mL of MeOH, 0.2 g of NH₄Cl and 40 mL of NH₄OH was stirred at 25°C for 48 hours with brief, intermittent warming at 50°C. The MeOH was partially removed, and the reaction mixture was diluted with H₂O. The solid precipitate was filtered, washed with H₂O and dried to give 4-(2-(2-phenyl-4-oxazolyl)ethoxy)-phenylacetamide (0.39 g, 82%, mp 180-183.5°C).

Elemental analysis for C₁₉H₁₉N₂O₃, Calcd.: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.54; H, 5.72; N, 8.50. FD-MS: m/e 322; NMR (DMSO-d₆): delta 2.968 (t, 2H), 3.250 (s, 2H), 4.214 (t, 2H), 6.788 (br.s, 1H), 6.865 (d, 2H), 7.350 (d, 2H), 7.354 (br.s, 1H), 7.493-7.504 (m, 3H), 7.928-7.954 (m, 2H), 9.008 (s, 1H).

H6
166

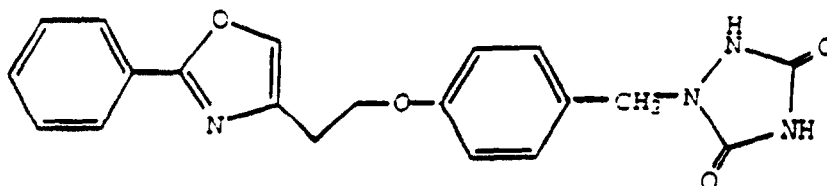
-45-

Part A. The mixture was stirred for 2.5 hours at 25°C and 25.0 g of diisopropylethyl amine was added followed by 3.70 mL of chlorocarbonylsulfenyl chloride. After stirring for 18 hours, the reaction mixture was poured into H₂O and extracted with EtOAc. The EtOAc layer was washed with H₂O, brine and dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvent, the dark oil was chromatographed on 220 g of silica. Elution with 1% MeOH in CH₂Cl₂ afforded 8.2 g of solid which was recrystallized twice from a mixture of CH₂Cl₂ and hexanes to give 7.40 g of 3-[(4-(2-(2-phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-thiadiazolin-5-one (41%, mp 160-163°C).

Elemental analysis for C₂₀H₁₇N₃O₃S. Calcd.: C, 63.31, H, 4.52, N, 11.07. Found: C, 63.10; H, 4.61; N, 11.07. FD-MS: m/e 379; NMR (DMSO-d₆): delta 2.991 (t, 2H), 3.746 (9s, 2H), 4.223 (t, 2H), 6.908 (d, 2H), 7.172 (d, 2H), 7.924-7.967 (m, 3H), 8.002 (s, 1H), 12.823 (br.s., 1H).

Example 17

20 Preparation of:
1-[(4-(2-(2-Phenyl-4-oxazolyl)ethoxy)phenyl)methyl]1,2,4-triazolidin-3,5-dione.



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H-7
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days, at which time TLC showed complete consumption of starting material. The cooled solution was acidified with 1N HCl and the resulting precipitate collected by filtration. Purification was effected by recrystallization from MeOH to provide 1.3 g (43%) of product as white needles, mp 179-181°C.

Anal. Cal. for C₂₆H₂₂N₄O₃: C, 71.22; H, 5.06; N, 12.78. Found: C, 71.11; H, 5.14; N, 12.97. IR: 1719cm⁻¹. MS: m/e 438. NMR: 3.97 (t, 2H), 3.73 (s, 2H), 4.19 (t, 2H), 6.78 (d, 2H), 6.85 (d, 2H), 7.22 (dd, 2H), 7.44 (m, 3H), 7.53 (m, 3H), 7.97 (m, 2H), 8.02 (s, 1H), 11.71 (s, 1H). exchanges with D₂O.

Testing Methods and Results

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Compounds were tested for antihyperglycemic activity according to the protocol described in A.M. Gill and T.T. Yen, "Effects of Ciglitazone on Endogenous Plasma Islet Amyloid Polypeptide and Insulin Sensitivity in Obese-Diabetic Viable Yellow Mice" Life Sciences 48, 703-710 (1991). The mice used in these tests were obese-diabetic viable yellow mice from the inbred Lilly colony. They were housed in transparent plastic cages with bedding. Purina Formula Chow 5008 (product of Purina Mills Inc., 717 South Hickory St., Fond Du Lac, WI 54935-5517 USA) and water were available ad libitum. The ambient temperature of the animal room was 25°C and lights were on from 0600 to 1800.

To study the effects of the candidate compounds, twelve male obese-diabetic viable yellow (VY) mice were divided into two groups for each candidate compound. One group was fed mesh or repelletized Purina 5008 Chow and one group was fed the same chow (mammal food) containing the indicated amount of candidate compound as set forth below in

-57-

the Table. Body weight and food consumption were monitored and blood samples collected before the experiment was initiated and after 14 days of treatment. In the Table, the blood glucose levels of mice given the test compounds are reported as a percentage of the initial value as compared to untreated controls on day 14 of treatment. Reductions of the initial values by less than 20% are regarded as inactive. The dose is the percent of compound incorporated into the feed (mesh or repelletized). The corresponding data for ciglitazone are included for comparison.

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TABLE

Example No.	Dose	BG%
1	.05	46%
2	.03	43%
3	.03	59
4	.05	49.5%
5	.03	27.4%
6	.05	39.5%
7	.03	33%
8	.03	70.5%
8A*	.03	97.6%
9	.03	55%
9A*	.05	82%
10	.05	46.1%
11	.05	51%
11A*	.05	109%
12	.03	43%
13	.03	40.7%
14	.05	34.7%
15	.03	40%
16	.03	47%
17	.05	41.8%
18	.03	57%
19	.03	54.4%
20	.03	28.2%
21	.03	53%
21A*	.03	99.5%
Cislitazone**	0.1	64%

* are comparative Examples to show
criticality of structure
** control experiment



US005103014A

United States Patent [19]

Musser et al.

[11] Patent Number: 5,103,014

[45] Date of Patent: Apr. 7, 1992

[54] CERTAIN
3,3'-[[[(2-PHENYL-4-THIAZOLYL)METHOX-
Y]PHENYL]METHYLENE]DITHIOBIS-
PROPANOIC ACID DERIVATIVES

[75] Inventors: John H. Musser, Yardley; Reinhold
H. W. Bender, Valley Forge;
Anthony F. Kreft, III, Langhorne;
James A. Nelson, Washington
Crossing, all of Pa.

[73] Assignee: American Home Products
Corporation, New York, N.Y.

[21] Appl. No.: 525,418

[22] Filed: May 18, 1990

Related U.S. Application Data

[60] Continuation-in-part of Ser. No. 311,558, Feb. 15, 1989,
Pat. No. 4,895,953, which is a division of Ser. No.
103,224, Sep. 30, 1987, Pat. No. 4,826,990.

[51] Int. Cl.⁵ C07D 277/30; C07D 277/32

[52] U.S. Cl. 548/204; 548/236;
548/342

[58] Field of Search 548/204

References Cited

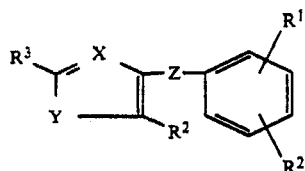
FOREIGN PATENT DOCUMENTS

0318085 5/1989 European Pat. Off. 548/204

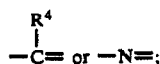
Primary Examiner—Alba L. Rotman
Attorney, Agent, or Firm—George Tarnowski

ABSTRACT

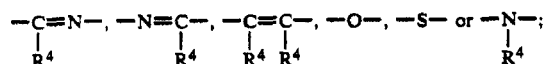
[57] There are disclosed compounds of the formula



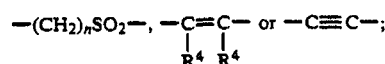
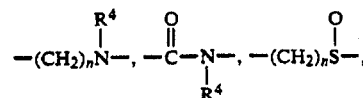
wherein
X is



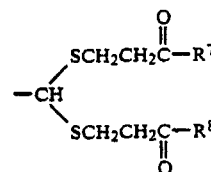
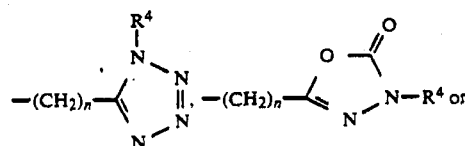
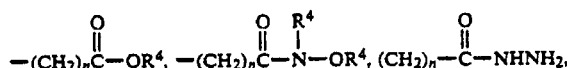
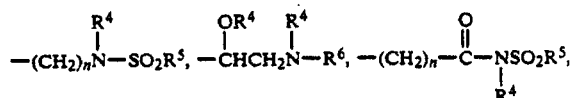
Y is



Z is $-(CH_2)_nO-$, $-(CH_2)_nS-$,



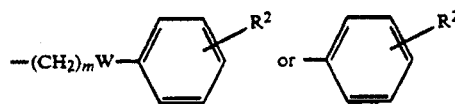
R¹ is



n is 0-5;

R² is hydrogen, loweralkyl, loweralkoxy, lower alk-
oxycarbonyl, trifluoromethyl, nitro, cyano or halo;

R³ is



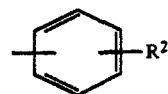
W represents a bond or $-O-$, $-S-$ or



m is 1-15;

R⁴ is hydrogen or loweralkyl;

R⁵ is lower alkyl, monofluoroloweralkyl, difluorolow-
eralkyl, polyfluoroloweralkyl, perfluoroloweralkyl
or



(Abstract continued on next page.)

CERTAIN
3,3'-[[[(2-PHENYL-4-THIAZOLYL)METHOXY]-
PHENYL]METHYLENE]DITHIOBIS-PROPANOIC
ACID DERIVATIVES

This application is a continuation-in-part of U.S. Ser. No. 311,558, filed Feb. 15, 1989 now U.S. Pat. No. 4,895,953, which is a division of U.S. Ser. No. 103,224, filed Sept. 30, 1987, now U.S. Pat. No. 4,826,990.

This invention relates to novel 2-aryl substituted heterocyclic compounds possessing lipoxigenase inhibitory and leukotriene antagonist activity, which are useful as anti-inflammatory and antiallergic agents.

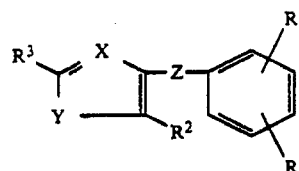
It is known that arachidonic acid (AA) is metabolized in mammals by two distinct pathways. The metabolism of arachidonic acid by cyclooxygenase enzymes results in the production of prostaglandins and thromboxanes. The physiological activity of the prostaglandins has already been amply elucidated in recent years. The other pathway of AA metabolism involves lipoxigenase enzymes and results in the production of a number of oxidative products called leukotrienes. The latter are designated by the LT nomenclature system, and the most significant products of the lipoxigenase metabolic pathway are the leukotrienes B₄, C₄, D₄ and E₄. The substance denominated slow-reacting substance of anaphylaxis (SRS-A) has been shown to consist of a mixture of sulfidopeptide leukotrienes, C₄, D₄ and E₄ [see Bach et al., *J. Immun.*, 215, 115-118 (1980); *Biochem. Biophys. Res. Commun.* 92, 1121-1126 (1980)].

The significance of these leukotrienes is that a great deal of evidence has been accumulated showing that leukotrienes participate in inflammatory reactions, exhibit chemotactic activities, stimulate lysosomal enzyme release and act as important factors in the immediate hypersensitivity reaction. It has been shown that LTC₄ and LTD₄ are potent bronchoconstrictors of the human bronchi [see Dahlen et al., *Nature*, 288, 484-486 (1980) and Piper, *Int. Arch. Appl. Immunol.*, 76, suppl. 1, 43 (1985)] which stimulate the release of mucus from airways in vitro [Marom et al., *Am. Rev. Resp. Dis.*, 126, 449 (1982)], are potent vasodilators in skin [see Bisgaard et al., *Prostaglandins*, 23, 797 (1982)], and produce a wheal and flare response [Camp et al., *Br. J. Pharmacol.*, 80, 497 (1983)]. The nonpeptide leukotriene, LTB₄, is a powerful chemotactic factor for leukocytes [see A. W. Ford-Hutchinson, *J. Roy. Soc. Med.*, 74, 831-833 (1981)], which stimulates cell accumulation and affects vascular smooth muscle [see Bray, *Br. Med. Bull.*, 39, 249 (1983)]. The activity of leukotrienes and mediators of inflammation and hypersensitivity is extensively reviewed in Bailey and Casey, *Ann. Reports Med. Chem.*, 17, 203-217 (1982) and in Bray, *Agents and Actions*, 19, 87 (1986).

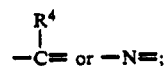
Accordingly, the biological activity of the leukotrienes and SRS's, and of lipoxigenase as the enzyme leading to the metabolism of AA to leukotrienes, indicates that a rational approach to drug therapy to prevent, remove or ameliorate the symptoms of allergies, anaphylaxis, asthma and inflammation must focus on either blocking the release of mediators of these conditions or antagonizing their effects. Thus, compounds which inhibit the biological effects of the leukotrienes and SRS's and/or which control the biosynthesis of these substances, as by inhibiting lipoxigenase, are considered to be of value in treating such conditions as

allergic bronchial asthma, allergic rhinitis, as well as in other immediate hypersensitivity reactions.

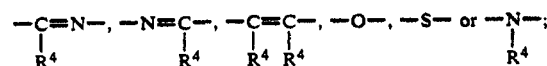
The invention provides novel compounds of the formula



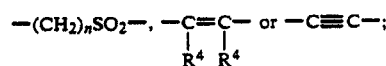
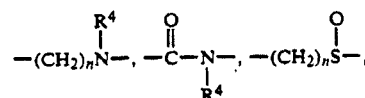
wherein
 X is



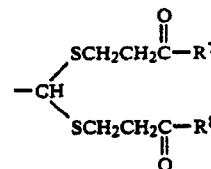
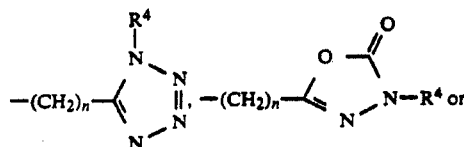
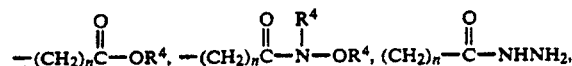
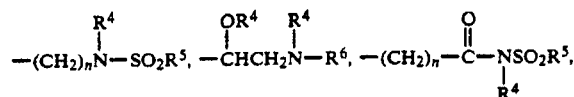
Y is



Z is $\text{---(CH}_2\text{)}_n\text{O---, ---(CH}_2\text{)}_n\text{S---,}$



R¹ is

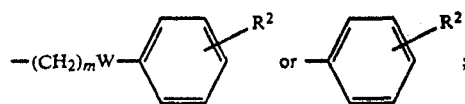


n is 0-5;

R² is hydrogen, loweralkyl, loweralkoxy, lower alkoxycarbonyl, trifluoromethyl, nitro, cyano or halo;

R³ is

3



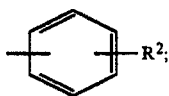
W represents a bond or $-O-$, $-S-$ or



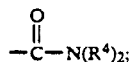
m is 1-15;

R^4 is hydrogen or loweralkyl;

R^5 is lower alkyl, monofluoroloweralkyl, difluoroloweralkyl, polyfluoroloweralkyl, perfluoroloweralkyl or



R^6 is hydrogen, lower alkyl, $-\text{COOR}^4$ or



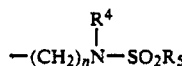
R^7 is OR^4 or $\text{N}(\text{R}^4)_2$;

R^8 is OR^4 or $\text{N}(\text{R}^4)_2$;

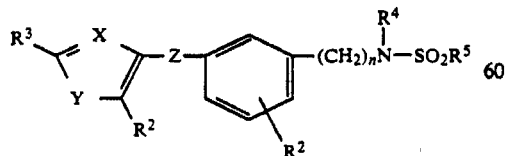
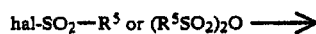
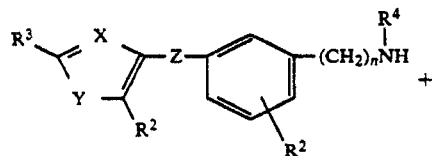
and the pharmaceutically acceptable salts thereof.

The term "halo" refers to fluoro, chloro, and bromo. The terms "loweralkyl" and "loweralkoxy" refer to moieties having 1-6 carbon atoms in the carbon chain.

The compounds of the invention can be prepared via variants of a basic reaction scheme using appropriate starting materials. Thus, compounds in which R^1 is the moiety



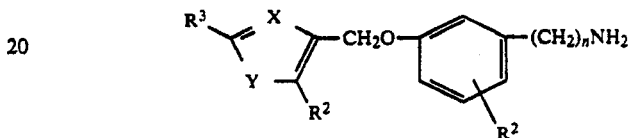
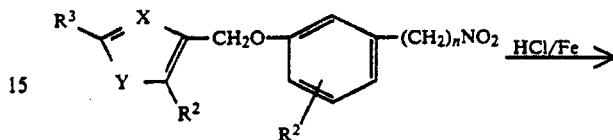
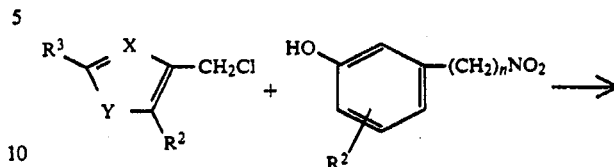
can be prepared by the reaction of an appropriate aniline derivative with an appropriate alkyl sulfonyl chloride or alkyl sulfonic anhydride as follows:



where X, Y, R^2 , R^4 , R^5 and n are as defined hereinbefore and hal refers to a halo radical, for example, chloro or bromo. The reaction is carried out in an organic solvent, for instance tetrahydrofuran, and at room tem-

4

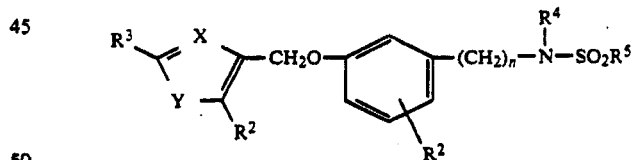
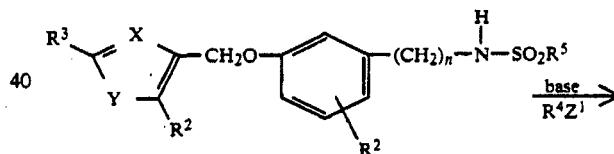
perature. The starting aniline derivatives employed in this reaction sequence and in which, for example Z is $-\text{CH}_2\text{O}-$, can be prepared as follows:



Additionally, those compounds in which R^1 is the moiety

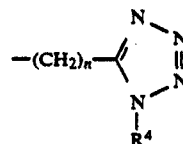


and R^3 is lower alkyl, can be readily prepared from the compounds wherein R^4 is lower alkyl by the following reaction sequence:

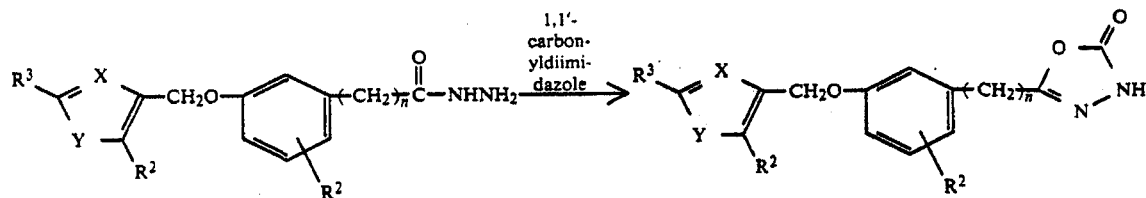


wherein X, Y, R^2 , R^4 , R^5 and n are as defined hereinbefore and Z^1 is the replaceable portion of the alkylating agent R^4Z^1 , which can be any of the conventional alkylating agents, such as for example the alkyl halides, alkyl sulfates, alkyl sulfonates and so forth.

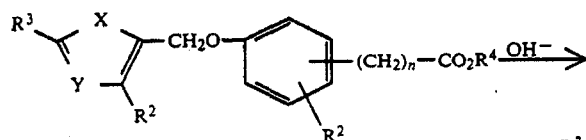
Compounds of the invention in which R^1 is



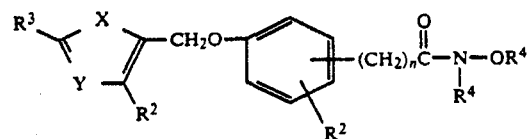
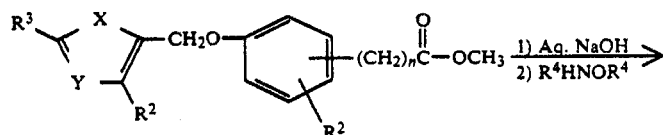
and R^4 is hydrogen, can be prepared by the following reaction scheme, where Z is again $-\text{CH}_2\text{O}-$:



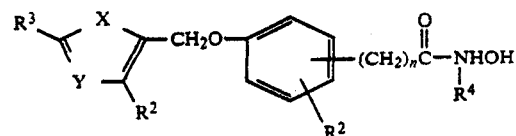
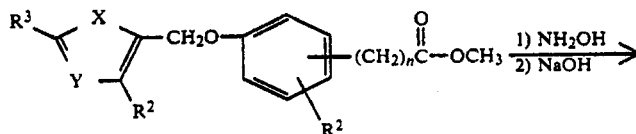
Alternatively, the carboxylic acid ester compounds can be hydrolyzed to the carboxylic acids, which can then be reacted with the appropriate sulfonamide reactants in order to obtain the desired sulfonylcarboxamide derivatives:



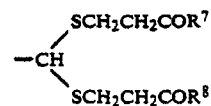
can be prepared using the carboxylic acid ester compounds described in the immediately preceding reaction sequences as starting compounds:



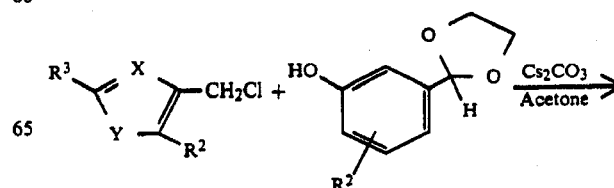
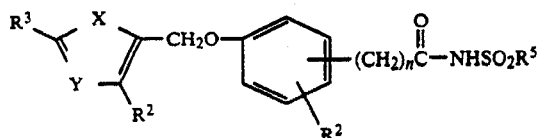
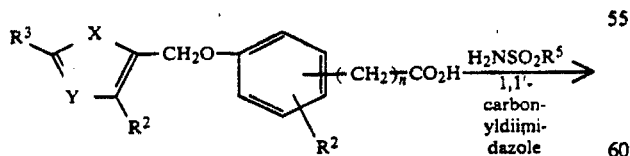
OR



Finally, compounds of the invention in which R¹ is



can be prepared by the following reaction sequence:



Compounds of the invention in which R¹ is

B. 1,1,1-Trifluoro-N-[3-[[2-(4-fluorophenyl)-4-thiazolyl]methoxy]phenyl]methanesulfonamide, m.p. 134°-136° C.

Analysis for: $C_{17}H_{12}F_4N_2O_3S_2$: Calculated: C, 47.22; H, 2.80; N, 6.48. Found: C, 47.24; H, 2.86; N, 6.38.

C. 1,1,1-Trifluoro-N-[3-[[2-(2-fluorophenyl)-4-thiazolyl]methoxy]phenyl]methanesulfonamide, m.p. 152°-154° C.

Analysis for: $C_{17}H_{12}F_4N_2O_3S_2$: Calculated: C, 47.22; H, 2.80; N, 6.48. Found: C, 47.46; H, 3.12; N, 6.55.

D.

1,1,1-Trifluoro-N-[3-[[2-(2,6-difluorophenyl)-4-thiazolyl]methoxy]phenyl]methanesulfonamide, m.p. 169°-172° C.

Analysis for: $C_{17}H_{11}N_2F_5O_3S_2$: Calculated: C, 45.33; H, 2.46; N, 6.22. Found: C, 45.55; H, 2.65; N, 6.18.

E. 1,1,1-Trifluoro-N-[3-[[2-(4-trifluoromethylphenyl)-4-thiazolyl]methoxy]phenyl]methanesulfonamide, m.p. 144°-146° C.

Analysis for: $C_{18}H_{12}F_6N_2O_3S_2$: Calculated: C, 44.81; H, 2.51; N, 5.81. Found: C, 44.89; H, 2.68; N, 5.63.

F. 1,1,1-Trifluoro-N-[3-[[2-(3-trifluoromethylphenyl)-4-thiazolyl]methoxy]phenyl]methanesulfonamide, m.p. 138°-142° C.

Analysis for: $C_{18}H_{12}F_6N_2O_3S_2$: Calculated: C, 44.81; H, 2.51; N, 5.81. Found: C, 44.77; H, 2.89; N, 5.84.

G. 1,1,1-Trifluoro-N-[3-[[2-(2-trifluoromethylphenyl)-4-thiazolyl]methoxy]phenyl]methanesulfonamide, m.p. 109°-111° C.

Analysis for: $C_{18}H_{12}F_6N_2O_3S_2$: Calculated: C, 44.81; H, 2.51; N, 5.81. Found: C, 44.89; H, 2.76; N, 5.81.

H. 1,1,1-Trifluoro-N-[3-[[2-(4-methoxyphenyl)-4-thiazolyl]methoxy]phenyl]methanesulfonamide, m.p. 154°-157° C.

Analysis for: $C_{18}H_{15}F_3N_2O_4S_2$: Calculated: C, 48.64; H, 3.40; N, 6.30. Found: C, 49.00; H, 3.29; N, 6.24.

I. 1,1,1-Trifluoro-N-[3-[[2-(benzyl)-4-thiazolyl]methoxy]phenyl]methanesulfonamide, m.p. 146°-149° C.

Analysis for: $C_{18}H_{15}F_3N_2O_3S_2$: Calculated: C, 50.46; H, 3.53; N, 6.54. Found: C, 50.31; H, 3.74; N, 6.22.

EXAMPLE 10

3-[[2-(2-Fluorophenyl)-4-thiazolyl]methoxy]benzoic acid hydrazide

A. 3-[[2-(2-Fluoromethyl)-4-thiazolyl]methoxy]benzoic acid methyl ester

A stirred mixture of 0.23 g (0.001 mol) of 4-[[3-(chloromethyl)phenoxy]methyl]-2-(2-fluorophenyl)-thiazole, 0.15 g (0.001 mol) of methyl-3-hydroxybenzoate and 0.32 g (0.001 mol) of cesium carbonate in 20 ml of acetone is heated under reflux for 3 hours. The mixture is filtered and the filtrate is evaporated in a rotary evaporator. The residue is recrystallized from heptane to give 0.09 g of product, m.p. 83°-86° C.

Analysis for: $C_{18}H_{14}FNO_3S$: Calculated: C, 62.96; H, 4.11; N, 4.08. Found: C, 63.40; H, 4.33; N, 4.33.

B. 3-[[2-(2-Fluorophenyl)-4-thiazolyl]methoxy]benzoic acid hydrazide

A stirred mixture of 5.0 g of 3-[[2-(2-fluoromethyl)-4-thiazolyl]methoxy]benzoic acid methyl ester in 70 ml of methanol containing 5 ml of hydrazine hydrate is heated under reflux for 24 hours. The mixture is cooled and the insoluble material is collected. The filter cake is recrystallized from acetonitrile to afford 3.5 g of title product, m.p. 143°-145° C.

Analysis for: $C_{17}H_{14}FN_3O_2S$: Calculated: C, 59.46; H, 4.11; N, 12.24. Found: C, 59.52; H, 4.29; N, 12.44.

EXAMPLE 11

5-[[3-[[2-(2-Fluorophenyl)-4-thiazolyl]methoxy]phenyl]-1,3,4-oxadiazol-2(3H)-one

A stirred mixture of 3.4 g (0.01 mol) of 3-[[2-(fluorophenyl)-4-thiazolyl]methoxy]benzoic acid hydrazide prepared according to Example 10 and 1.6 g (0.01 mol) of 1,1'-carbonyldiimidazole in 50 ml of dichloromethane is heated under reflux for 3 hours. The mixture is evaporated in a rotary evaporator and the residue is recrystallized from ethanol to provide 2.5 g of title product, m.p. 198°-202° C.

Analysis for: $C_{18}H_{12}FN_3O_3S$: Calculated: C, 58.53; H, 3.28; N, 11.38. Found: C, 58.79; H, 3.53; N, 11.47.

EXAMPLE 12

3,3'-[[3-[[2-(Phenyl-4-thiazolyl)methoxy]phenyl]methylene]dithiobis[propanoic acid]dimethyl ester

A. 4-Chloromethyl-2-phenylthiazole

A mixture of thiobenzamide (13.7 g, 0.10 mol), 1,3-dichloroacetone (12.7 g, 0.10 mol), sodium bicarbonate (8.4 g, 0.10 mol) and dichloroethane (200 mL) is refluxed for 6 hours. The reaction mixture is cooled to 23° C. and the solid by-products are removed by filtration. The filtrate is concentrated under reduced pressure to give the crude product (19.0 g). This material is recrystallized from hexane and the title product is obtained as a light yellow solid (18.2 g) in 86.0% yield, m.p. 44°-48° C.

B.

4-[[3-(1,3-Dioxolan-2-yl)phenoxy]methyl]-2-phenylthiazole

A mixture of 4-chloromethyl-2-phenylthiazole (13.7 g, 0.0653 mol), 1-(1,3-dioxolan-2-yl)-3-hydroxybenzene (13.6 g, 0.0817 mol (25% excess)), cesium carbonate (26.7 g, 0.082 mol) and dimethylsulfoxide (70 mL) is heated at 45° to 50° C. for 2 hours. The reaction mixture is slowly poured into ice water (500 mL). The aqueous dimethyl sulfoxide solution is extracted three times with ether (600 mL). The combined ether solution is washed with 0.5N NaOH (500 mL), brine (twice, 500 mL) and dried over $MgSO_4$ and silica gel (10 g). The solids are filtered and the filtrate is concentrated under reduced pressure to a volume of ca. 400 mL. The product crystallizes from the ether solution and after filtration, is obtained as a light yellow solid (13.0 g). Upon further concentration of the filtrate, an additional 6 g of product is isolated, m.p. 77°-79° C.

^1H NMR ($CDCl_3$): δ 8.0-7.0 (m, 10H), 5.8 (s, 1H), 5.3 (s, 2H), 4.15-4.0 (m, 4H).

IR (KBr): 1610 cm^{-1} .

Analysis for: $C_{19}H_{17}NO_3S$: Calculated: C, 67.24; H, 5.05; N, 4.13. Found: C, 67.34; H, 5.07; N, 4.17.

C.

3,3'-[[3-[[2-(Phenyl-4-thiazolyl)methoxy]phenyl]methylene]dithiobis[propanoic acid]dimethyl ester

A mixture of the acetal (3.4 g, 0.010 mol) of Step B, methyl mercaptopropionate (2.7 g, 0.022 mol) and methylene chloride (20 mL) is cooled to 0° C. and a solution containing $BF_3 \cdot Et_2O$ (3.7 mL, 0.030 mol) and methylene chloride (10 mL) is added slowly. After the addition of the $BF_3 \cdot Et_2O \cdot CH_2Cl_2$ solution, the reaction

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES

2020
Bogotá, D.C.

Abogado
EMILIO FERRERO

ASUNTO Radicación 06-098507
 Trámite 011
 Evento 378
 Actuación 411
 Oficio 04851
 Folios 026

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☒ Cap. II ☐
No. Sol. Internacional PCT/US2005/010854
Fecha de Presentación Internal. 30-05-2005

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

1. Documentos estudiados

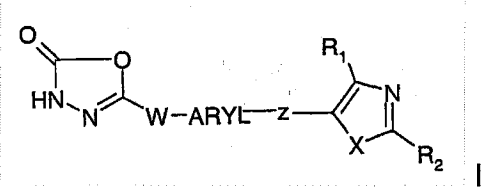
Descripción: Folios 66-100 como se radicó inicialmente
Reivindicaciones: Folios 101-103 como se radicó inicialmente
Prioridad: Folio 1 US, 60/558419, 01-04-2004

2. Objeto de la invención

Título de la solicitud: 1,3,4-OXADIAZOL-2-ONAS COMO MODULADORES DEL PPAR DELTA Y LOS USOS DE LAS MISMAS (folio 1)

El problema técnico planteado en la solicitud está relacionado con la necesidad de obtener nuevos compuestos moduladores de receptores PPAR delta (receptores activados por proliferadores de peroxisoma), útiles en el tratamiento del metabolismo de ácidos grasos y trastornos de la utilización de la glucosa; tales como dislipidemias y diabetes mellitus, entre otras (folios 67; pág. 3-4).

Para solucionar este problema técnico la solicitud en estudio proporciona en: Reivindicaciones 1-16: un compuesto de fórmula I ó un estereoisómero, un tautómero o un solvato del mismo o una sal farmacéuticamente aceptable del mismo.



Reivindicación 17: una composición farmacéutica que comprende un compuesto de formula I y un vehículo farmacéuticamente aceptable.

Reivindicaciones 18-21: relacionada con un método de tratamiento.

Clasificación Internacional de Patentes (IPC): C07D417/12, A61K31/4245, A61P3/06.

3. De la solicitud de Patente

3.1 Reivindicaciones (artículo 30 D 486)

Se solicita en las reivindicaciones 1-16 un compuesto de fórmula I con radicales R^1 , R^2 y ARIL y variables W, X y Z, ó un estereoisómero, un tautómero o un solvato del mismo o una sal farmacéuticamente aceptable del mismo; No obstante, existe falta de claridad, concisión y sustento de la materia solicitada, puesto que:

- Se solicitan solvatos farmacéuticamente aceptables del compuestos de formula (I), pero no se encuentra soporte de ningún solvato en los compuestos ejemplificados en la descripción; por lo tanto, el término solvato debe ser eliminado.

- Existe falta de soporte para la amplia materia solicitada y de acuerdo con los 8 compuestos sintetizados ejemplificados (ej. 10, 11, 14, 17, 23, 28, 31 y 34) solo se encuentra soporte para los siguientes radicales:

W: enlace o $(CH_2)_m$ con m: 1 o 2

ARIL: fenilo opcionalmente sustituido por Cl o F

Z: $-OCH_2-$ ó $-CH_2-O-CH_2-$

X: O ó S

R^1 : alquilo $C_{1,4}$

R^2 : fenilo opcionalmente sustituido por $-CF_3$

Por lo anterior, el capítulo reivindicatorio no cumple con el requisito de tener claridad, concisión y soporte de acuerdo con las exigencias del artículo 30 de la Decisión 486.

4. Excepción a la patentabilidad (artículo 20 D486 literal d)

Las reivindicaciones 18-21, relacionadas con un método de tratamiento, están exceptuadas de patentabilidad de acuerdo con el artículo anterior; por lo que es necesario eliminarlas del alcance de la solicitud.

5. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la que se reivindica prioridad es 01-04-2004, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a ésta.

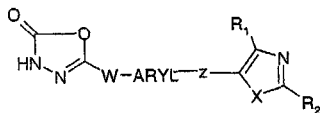
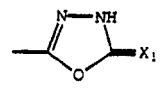
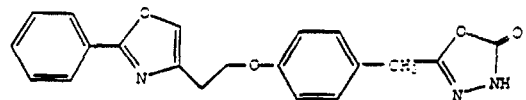
Nº	Documento	Título	Fecha de Publicación
D1	WO9613264	Oral hypoglycemic agents	09-05-1996
D2	US5103014	Certain 3,3'-[[[(2-phenyl-4-thiazolyl)methoxy]phenyl]methylene]dithiobispropanoic acid derivatives.	07-04-1992

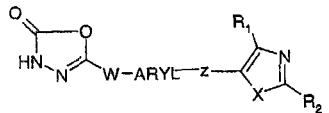
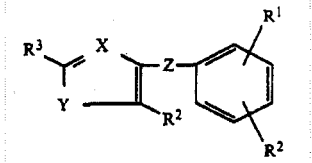
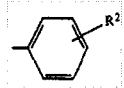
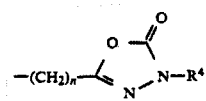
Anterioridad D1 en folios 152-169 y D2 en folios 170-174.

6. Análisis de patentabilidad (artículo 14 D486)
6.1 Novedad (artículo 16 D486)

Se solicita en las reivindicaciones 1-16 un compuesto de fórmula I con radicales R¹, R² y ARIL y variables W, X y Z, ó un estereoisómero, un tautómero o un solvato del mismo o una sal farmacéuticamente aceptable del mismo; y en la 17 una composición farmacéutica que lo contiene junto con un vehículo farmacéuticamente aceptable.

Al comparar elemento por elemento el objeto de la presente solicitud con el estado, se encuentra que:

SOLICITUD	D1
Un compuesto de fórmula I  con radicales R ¹ , R ² y ARIL y variables W, X y Z según capítulo reivindicatorio.	Un compuesto de la siguiente formula (folios 156-159; pág. 4-7.) $\text{Ar}-(\text{G})_{n-1}-(\text{CH}_2)_{m-1}-\text{CH}_2\text{Z}$ Donde m: 1 y n: 1, quedando la formula: Ar-CH₂-Z Ar: Y-(CH ₂) _p -(G')-Ar' Y: heterociclilo como 2-fenilo-4-oxazolilo p: 1-6 G': O Ar': fenileno, metilfenileno, clorofenileno, etc. Z: pentacicloazol C-sustituido de formula I  con Q: C, N, O ó S, incluyendo el ciclo:  con X1: O Obteniendo compuestos como el del ej. 13 (folio 163; pag.39): 

SOLICITUD	D2
Un compuesto de fórmula I  con radicales R ¹ , R ² y ARIL y variables W, X y Z según capítulo reivindicatorio.	Un compuesto de la siguiente formula (folios 171-172; col. 2-3)  R ³ :  R ² : H, halógeno, alquilo, alcoxi, alcoxycarbonilo, -CF ₃ , NO ₂ o CN X: N Y: O, S ó -NR ₄ , con R ₄ : H ó alquilo Z: -(CH ₂) _n O-, (CH ₂) _n SO ₂ , con n: 1-5 R ¹ :  con n: 0-4 y R ₄ : H

Incluyendo así compuestos como el de la siguiente formula (folio 173; col. 10):

R3C(X)C(Y)C(R2)COc1ccc(cc1)CNC(=O)O

con R², R³, X, Y y n como se indico arriba

Y compuestos específicos como el del ej. 11 (folio 174; col.29):
5-[3-[[2-(2-fluorofenil)-4-tiazolil]metoxi]fenil]-1,3,4-oxadiazol-2(3H)-ona

Fc1ccccc1-c2nc(COc3ccc(cc3)-c4nn[nH]4)cs2

Tanto D1 como D2 divulgan compuestos incluidos en la solicitud, tal como se explica arriba en el cuadro comparativo; por consiguiente, la materia solicitada (un compuesto de formula I y composiciones farmacéuticas que lo contienen) no cumple el requisito de novedad.

7. Conclusión

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

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO9613264	1-17	Novedad
D2	US5103014	1-17	Novedad

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

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
09 ABR. 2010

CONCEPTO TECNICO No. 977	EXAMINADOR TECNICO Código No. 202079
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EXAMEN TÉCNICO DE FONDO

Nº Radicación	06-93505	Fecha de presentación	2006-09-29
Nº Solicitud Internacional	PCT/US2005/010854	Fecha Solicitud Internacional	30-05-2005
Nº Prioridad	US, 60/558419	Fecha de Prioridad	01-04-2004

Palabras clave	SOLICITANTE: AVENTIS PHARMACEUTICALS INC.
INVENTOR: MCGARRY DANIEL G [US]; GOERLITZER JOCHEN [DE]; KEIL STEFANIE [DE]; CHANDROSS KAREN [US]; MERRILL JEAN [US]; WENDLER WOLFGANG	
Fenil-tiazolil-metoxi-fenil-1,3,4-oxadiazol-2(3H)-ona	hypoglycemic agents
Oxazole ppar antagonists	Compuestos moduladores del receptor activado por proliferador de peroxisoma (PPAR)

CLASIFICACIONES INTERNACIONALES DE BÚSQUEDA

C07D417/12, A61K31/4245, A61P3/06

FAMILIA DE PATENTES

Family list

13 application(s) for: WO2005097762 (A2)

AU2005230837 (A1) - 2005-10-20	KR20060135854 (A) - 2006-12-29	WO2005097762 (A2) - 2005-10-20
BRPI0509468 (A) - 2007-09-11	NO20064982 (A) - 2006-10-31	WO2005097762 (A3) - 2005-12-15
CA2561738 (A1) - 2005-10-20	NZ550857 (A) - 2009-12-24	ZA200607851 (A) - 2008-06-25
CN1938305 (A) - 2007-03-28	RU2006138485 (A) - 2008-05-10	
CN100516065 (C) - 2009-07-22	RU2375358 (C2) - 2009-12-10	
EP1735303 (A2) - 2006-12-27	US2007060626 (A1) - 2007-03-15	
JP2007531763 (T) - 2007-11-08	US7576109 (B2) - 2009-08-18	

BASES DE DATOS CONSULTADAS

WIPO PATENSCOOP	USPTO	ESPACENET	EPOLINE
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INFORMES DE EXÁMENES EN OTRAS OFICINAS

Oficina	Fecha	Reiv. afectadas
EPO	ISR	19-09-2005
EPO	IPER	24-10-2006

ANTERIORIDADES ENCONTRADAS

Documento	Reiv. afectadas	Relevancia
WO0078313 (A1) 2000-12-28	Arylthiazolidinedione and aryloxazolidinedione derivatives	
WO0100603 (A1) 2001-01-04	Thiazole and oxazole derivatives and their pharmaceutical use	
WO0117994 (A1) 2001-03-15	Oxazole ppar antagonists	
WO9613264 09-05-1996	Oral hypoglycemic agents	1-17
US5103014 07-04-1992	Certain 3,3'-[[[(2-phenyl-4-thiazolyl)methoxy]phenyl]methylene]dithiobispropanoic acid derivates.	1-17
WO2005097763 (A2) - 2005-10-20 ó CO06-98503: solicita materia de la presente solicitud, pero fechas de prioridad y presentación son iguales a solicitud, entrando primero la solitud.	1,3,4-oxadiazol-2-ones as ppar delta modulators and their use thereof	

LITERATURA NO PATENTES

[Y] S. S. KULKARNI ET AL.: "Three-Dimensional Quantitative Structure Activity Relationship (3-D-QSAR) of Antihyperglycemic Agents" BIOORG. MED. CHEM., vol. 7, 1999, pages 1475-1485, XP002345584

[A] B. R. HENKE ET AL.: "N-(2-Benzoylphenyl)-L-tyrosine PPAR.gamma. Agonists. 1. Discovery of a Novel Series of Potent Antihyperglycemic and Antihyperlipidemic Agents" J. MED. CHEM., vol. 41, no. 25, 11 November 1998 (1998-11-11), pages 5020-5036, XP000864731

Documento	Relevancia	Reiv. afectadas
Observaciones		
1er Art 45		
Fecha del examen	03-2010	