



Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

06-78216

21. EXPEDIENTE No.

54. TÍTULO Derivados de 1,3-Dioxano y análogos de éstos útiles en el tratamiento de obesidad y diabetes entre otros

51. CLASIFICACIÓN INTERNACIONAL C07D 405/06 413/06 495/04
417/06 495/04 417/06 407/06 A61K 31/357

71. SOLICITANTE Cadila Healthcare limited

DOMICILIO Gujarat, India.

74. APODERADO Julia Maria Rodriguez D'Alencar

22. BOGOTÁ, D. C., Agosto 9/06.

**FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT**

ENTRADA EN FASE NACIONAL

09/08/06

1) SOLICITUD DE:			
☒ Patente de invención		☐ Patente de Modelo de Utilidad	
☐ Capítulo I.		☒ Capítulo II.	
2) SOLICITANTE (71)	Nombre: CADILA HEALTHCARE LIMITED		IDENTIFICACIÓN C.C. ☐ NIT ☐ C.E. ☐ OTRO ☐ Cual _____ NÚMERO _____
	Dirección: Zydus Tower, Satellite Cross Road, Ahmedabad 380 015, Gujarat, India Nacionalidad o domicilio: Gujarat, India Lugar de constitución: India		
	Teléfono: _____ Fax: _____ E. Mail: _____		
3) REPRESENTANTE O APODERADO	Nombre: DILIA MARIA RODRIGUEZ D'ALEMAN		IDENTIFICACIÓN C.C. ☒ NIT: ☐ C.E. ☐ OTRO ☐ NÚMERO: 41.654.882 TP: 20824 CSJ
	Dirección: Carrera 11 N°. 86-53 Piso 6 Bogotá D.C. Teléfono: 6181088 Fax: 6350824 E. Mail: info@clarkemodet.com.co		
4) INVENTOR (ES) (72)	Nombre: 1. LOHRA, Braj, Bhushan; 2. LOHRAY, Vidya, Bhushan. Dirección: 1 y 2 . Cadila Healthcare Limited, Zydus Tower, Satellite Cross Road, Ahmedabad 380 015, Gujarat, India Nacionalidad o Domicilio: 1 y 2 Hindúes		
5) PCT (86) Solicitud Internacional No. PCT/IN2005/000011 Fecha: Enero 7, 2005 Publicación Internacional No. WO2005/077943 A1 Fecha: Agosto 25, 2005			
6) Título (54) DERIVADOS DE 1, 3 – DIOXANO Y ANÁLOGOS DE ÉSTOS ÚTILES EN EL TRATAMIENTO DE OBESIDAD Y DIABETES ENTRE OTROS			
7) Clasificación Internacional: C07D 405/06, 319/06, 413/06, 495/04, 417/06, 407/06, A61K 31/357, A61P 3/04, C07D 405/12			
8) PRIORIDAD		33) País de Origen	(32) Fecha
SI ☒ NO ☐		India	Enero 9, 2004
			(31) Número de Solicitud 23/MUM/2004
9) Comprobante de pago N°. 06-54,185 Fecha: Julio 17 de 2006			
Instrucciones para el diligenciamiento del presente formulario Ver reverso de esta pagina			

7814 2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-078216-00000-0000
Fec 2006-08-09 15 00 11 Dep 2020 NUECREACIONES
Tra 11 PATENTEYII
Eva 379 FASENACIONALI
Act 411 PRESENTACION Folios 165

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 54,185
FECHA : JULIO 17 DE 2006

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MCDET Y CO. COLOMB	CONSIGNACION	BANCO POPULAR	050-00110-6	48147155	17/07/2006	4,000,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
1		TRANITES DE SOL. DE PATENTE DE IN	463,000.00
		TOTAL :	\$ 463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

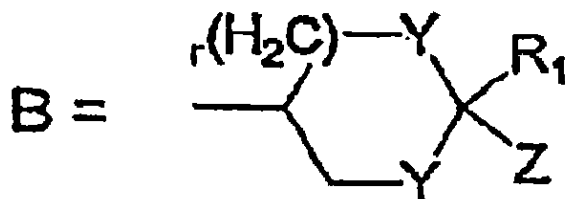
RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

10)

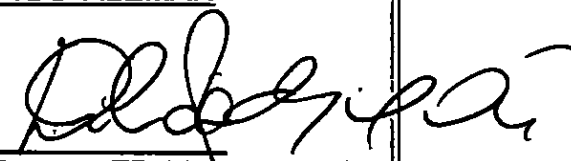
ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
☐ Comprobante de pago por reivindicación de prioridad
☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
☒ Poderes, si fuera el caso
☐ Documento de cesión del inventor al solicitante o a su causante
☐ Declaraciones
☒ Copia de la solicitud Internacional (Resumen, descripción, reivindicación, Dibujos)
☒ Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicación, Dibujos)
☒ Copia del examen preliminar efectuado por la IPEA
☐ De ser el caso, copia del contrato de acceso
☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
☐ De ser el caso, certificado de depósito del material biológico
☐ Arte final 12 x 12 y 6 x 6 cm
☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud
☒ Otros
- 1 Reporte internacional de búsqueda
 - 2 documentos informe de búsqueda
 - 3 Opinión escrita

11) FIGURA CARACTERÍSTICA:



12) Solicitud concesión de la patente,

NOMBRE: DILIA RODRÍGUEZ D'ALEMANFIRMA: 

C.C. 41.654.882 de Bogotá TP 20824 CSJ

Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta página

TRADUCCIÓN OFICIAL No 02/329 de un documento escrito en inglés, el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Juan Pablo Piedrahita Aguilera, Traductor e Intérprete Oficial debidamente reconocido de conformidad con el Certificado de Idoneidad Profesional No. 0045 expedido por la Universidad Nacional de Colombia.

(Se traducen los sellos sobre un poder otorgado por la compañía CADILA HEALTHCARE LIMITED con fecha Septiembre 21, 2002, escrito en inglés y español, y Legalización No. 516875 Ministerio de Relaciones Exteriores).

(En ingles y español, poder)

(Sello No. de Serie 313, 2002, (Firma) R. J. BRAHMBHATT, NOTARIO, GOBIERNO DE GUJARAT)

(Sello Notarial a Tinta, Mi Comisión vence 10/07/2007, (Firmado) R.J. BRAHMBHATT, Notario, Gobierno de Gujarat)

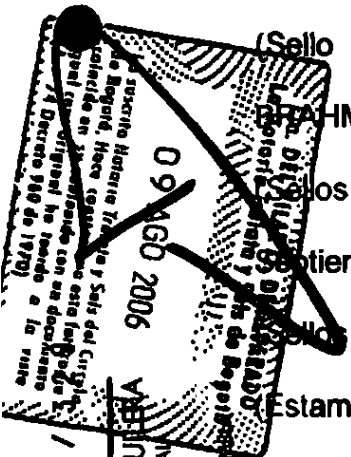
(Sellos a tinta de la Cámara de Comercio e Industria de Nueva Delhi, 26 de Septiembre 2002)

(Sellos a Notariales a tinta del Gobierno de Gujarat, 21 de Septiembre 2002)

(Estampillas)

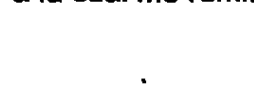
(Sello Notarial a Tinta, Ante mi, (Firmado) R.J. BRAHMBHATT, Notario, Gobierno de Gujarat)

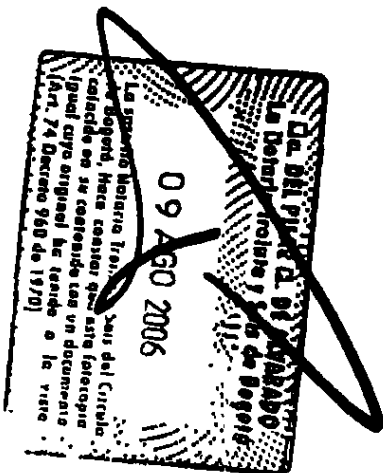
Al respaldo: (Sellos a Tinta autenticando la firma del Funcionario de la Cámara

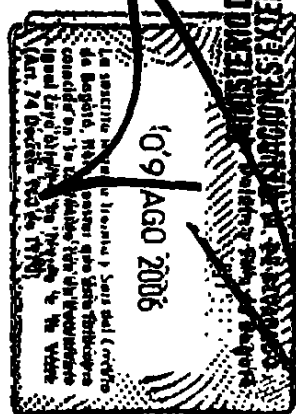


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 09 AGO 2006
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 UNIVERSIDAD NACIONAL DE COLOMBIA

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 TRADUCTOR E INTERPRETE OFICIAL
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 UNIVERSIDAD NACIONAL DE COLOMBIA





MINISTÈRE DE LA SANTÉ DES SERVICES MÉDICAUX DES SERVICES DE RÉFÉRENCE

09 AGO 2006

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172002
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

**NO SE ASUME
RESPONSABILIDAD DEL TEXTO**

7997 OCT 30 P 12:36

**JEFE DE LEONIZACIONES
BOGOTÁ D.C.**

COLOMBIA

Carrera 11 n° 93-43, Of 404 Bogotá Colombia Tel. (57 1) 6350813-Fax: (57 1) 6350824 Email:clarkemodetclarkemodet.com.co

R. J. BRAHMBHATT
NOTARY
GOVT. OF GUJARAT

PODER

Yo (nosotros), abajo firmante(s)

Arun Madhusudan Parikh

en mi (nuestro) carácter de representante(s) legales de

Cadila Healthcare Limited

una sociedad organizada y existente de acuerdo con las leyes de *India*.

y en actual cumplimiento de su objeto social, con domicilio en *Zydus tower Satellite Road, Ahmedabad, India*
Pin 380015

por el presente instrumento confiero (conferimos) poder especial a favor de DILIA MARIA RODRIGUEZ D'ALEMAN, con Cédula de Ciudadanía No 41.654.882 de Bogotá, y tp 20824 y CLAUDIA LUCIA CARO RAMIREZ, con Cédula de Ciudadanía No 40 017.374 de Tunja, y tp 36448, con domicilio en Bogotá, Colombia, para que actuando en su orden en nombre del (de la) otorgante le (la) representen ante cualquier entidad, autoridad y/o persona, especialmente ante las del orden Administrativo, Contencioso Administrativo, Judicial, Tribunales de Arbitramento y/o cualquier otro en lo referente a los siguientes asuntos

- 1) Solicitar, tramitar, obtener y/o registrar cualquiera de las modalidades de Propiedad Industrial, tales como patentes de invención, modelos de utilidad; diseños industriales, variedades vegetales, marcas, lemas, nombres y enseñanzas comerciales y denominaciones de origen, así como sus renovaciones, prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias
- 2) Solicitar, tramitar, obtener y/o registrar derechos de autor, en cualquiera de sus presentaciones así como la obtención de secretos industriales y know-how
- 3) Solicitar, tramitar, obtener y/o registrar registros sanitarios, permisos y/o licencias de funcionamiento, así como sus renovaciones o prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias
- 4) Ejercer acciones de oposición, observación,

POWER OF ATTORNEY

I (we), the undersigned

ARUN MADHUSUDAN PARIKH

legal representative(s) of

CADILA HEALTHCARE LIMITED

an organization existing under the laws of

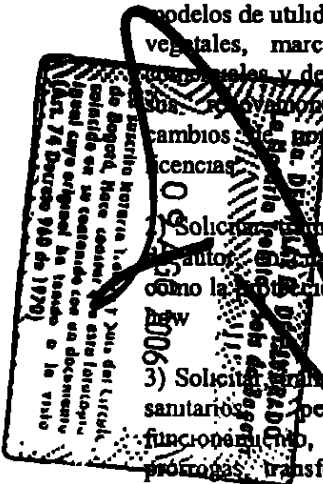
INDIA

and in present execution of its business activity, domiciled at

ZYDUS TOWER, SATELLITE ROAD, AHMEDABAD, GUJARAT, INDIA.
PIN: 380015

do hereby grant POWER OF ATTORNEY to DILIA MARIA RODRIGUEZ D'ALEMAN, identification card No. 41.654.882 of Bogotá, and tp. 20824 and CLAUDIA LUCIA CARO RAMIREZ, tp. 36448, identification card No 40 017 374 of Tunja, residing in Bogotá, Colombia, to act in the order of their appointment in behalf of grantor before any entity, authority and/or natural or juridical person, specially before those Administrative, Administrative-Contentious, Judicial, arbitration courts, and/or any other, in all matters concerning the following:

- 1) To apply, process, obtain and/or register any of the modalities of Industrial Property, such as: Patents of Invention, Utility Models, Designs, plant varieties, Marks, Slogans, Trade Names and emblems and appellations of Origin, as well as their renewals, extensions, assignments, changes of name and/or domicile, agreements and licenses
- 2) To apply, process, obtain and/or register copyrights of any kind as well as protection of industrial secrets or know-how.
- 3) To apply, process, obtain and/or register sanitary registrations, operating authorizations and/or licenses, as well as their renewals or extensions, assignments, changes of name and/or domicile, agreements and licenses
- 4) To bring actions of opposition, observations, claims, reconsideration, appeal or legal remedies, cancellations, nullity, protection to the consumer, granting of licenses, protection of trade secrets and other actions related with rights derived from the



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reclamados, reconsideración, reposición, apelación, cancelación administrativa o judicial, nulidad, protección al consumidor, concesión de licencias, protección de secretos industriales y demás acciones y recursos relacionados con derechos derivados de los asuntos arriba indicados y en contra de la competencia desleal, acciones derivadas de la obtención o explotación de licencias, acciones de indemnización de perjuicios También podrá(n) intervenir en juicios civiles, comerciales, penales, contencioso-administrativos, tutelas y de policía, en acciones o juicios promovidos por el (la) mandante o en contra el (ella)

5) Registrar nombres de dominio ante la entidad competente

6) En el ejercicio de este mandato los mandatarios arriba mencionados quedan facultados para: conciliar, cancelar, transigir, comprometer en árbitros, desistir, recibir y tomar posesión de la cosa objeto de litigio y renunciar o desistir a derechos concedidos o en curso de concesión, admitir los hechos del proceso.

7) Ratificar o no la agencia oficiosa.

8) Así mismo faculto (facultamos) a los mencionados apoderados para recibir notificaciones y designar apoderados judiciales o extrajudiciales, sustituir el presente poder y revocar las sustituciones que hicieren

Dado y firmado en

a los 21 días de Sept. 2002

competition, actions resulting from the obtaining or exploitation of licenses, recovering damages actions They can also intervene or participate in Civil, Commercial, Criminal or Contentious-Administrative Trials; the actions for writ mandamus, police actions; in actions, lawsuits or litigations instituted by the grantor or against him

5) To register domain names before the competent entity.

6) To the effect of this mandate the above-named proxy are empowered to. conciliate, cancel, settle, submit to arbitration, withdraw and to receive and take possession of the litigation related object and waive or renounce the rights granted or in process of granting, admit the facts of the case.

7) To ratify or not the officious agency.

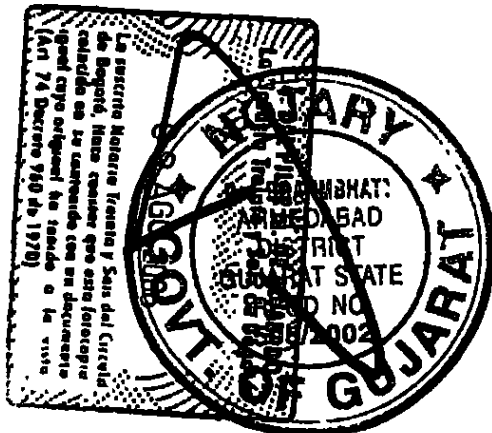
8) I (we) hereby appoint the afore mentioned attorneys with powers to receive notifications and to designate judicial and extra-judicial attorneys, substitute this Power of Attorney and to revoke such substitutions

Granted and signed at

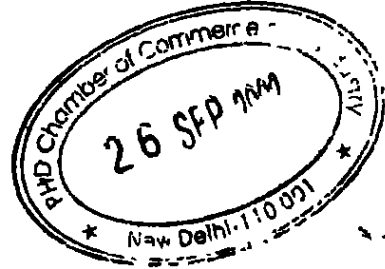
on this 21st day of SEPTEMBER, 2002.

Firma/ Signature

[Handwritten Signature]

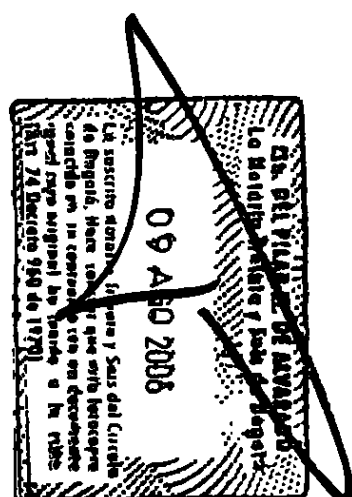


BEFORE ME
[Signature]
R. J. BRAHMBHATT
NOTARY
GUJARAT



ATTESTED
[Signature]
Addl./Jointly /Sr. Asst. Secretary General/Admn. Officer
PHD Chamber of Commerce and Industry
New Delhi

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JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
C IDONEIDAD 045
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TRANSMISSION OFFICIAL
JU
GUILERA
OFFICIAL
2006-03-25
COLOMBIA

No 13997 Date 27 SEP 2006
बाह्यविषय मन्त्रालय के सहायक सचिव/उप सचिव /
सचिव की हस्ताक्षर सत्यापित किये जाते हैं।
The Signature of Asstt. Secretary /
Asstt. Secretary / Secretary of Charge
is hereby authenticated



(ए. ई. ओश)
(A. E. OHOSH)
सहायक अधिकारी (ओ.ई.)
Section Officer (O.I.)
हिन्दू मंत्रालय, नई दिल्ली
Ministry of External Affairs
New Delhi

No.19/2002

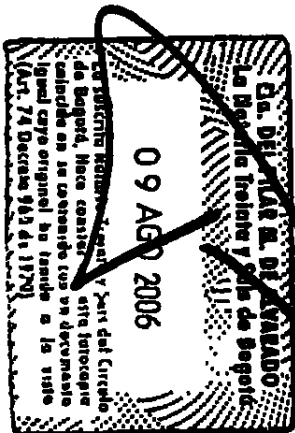
EL SUSCRITO MINISTRO PLENIPOTENCIARIO ENCARGADO DE LAS
FUNCIONES CONSULARES ANTE LA EMBAJADA DE COLOMBIA EN NUEVA
DELHI INDIA,

VISTOS LOS DOCUMENTOS PRESENTADOS POR LOS INTERESADOS

CERTIFICA:

QUE EL SEÑOR A.K. GHOSH, FUNCIONARIO CONSULAR DEL
MINISTERIO DE RELACIONES EXTERIORES DE INDIA, QUIEN
AUTENTICO LA FIRMA DEL SEÑOR ARUN MADHUSUDAN PARIKH,
FIRMANTE DEL PRESENTE DOCUMENTO, EJERCIÓ EN LA FECHA
LAS FUNCIONES INDICADAS Y SU FIRMA CORRESPONDE A LA
REGISTRADA EN ESTE CONSULADO; QUE LA COMPAÑIA CADILA
HEALTHCARE LIMITED* ESTA CONSTITUIDA DE ACUERDO CON LAS
LEYES DE LA INDIA Y CUMPLE SU OBJETO CONFORME A LAS
MISMAS. DOMICILIADA EN AHMEDABAD GUJARAT, INDIA; QUE EL
SEÑOR ARUN MADHUSUDAN PARIKH, EN SU CARACTER DE VICE-
PRESIDENTE Y REPRESENTANTE LEGAL DE LA EMPRESA ARRIBA
MENTIONADA, ESTA FACULTADO PARA FIRMAR EL PRESENTE
DOCUMENTO.

DADO EN NUEVA DELHI A LOS TRES (3) DIAS DEL MES DE OCTUBRE
DE DOS MIL DOS (2002).



[Signature]
LUIS GUILLERMO BECERRA
Ministro Plenipotenciario
Cónsul de Colombia



[Signature]
518875
Luís G. Becerra
COTA FIRMA ADECUADA EN EL
DOCUMENTO PRESENTADO
LAS FUNCIONES INDICADAS

MINISTERIO DE RELACIONES
EXTERIORES

PAGADO IMPUESTO DE TIMBRE Y
DERECHOS CONSULARES: US \$108.00
(Ciento ocho Dólares Americanos)

UNIVERSIDAD NACIONAL DE COLOMBIA

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JUAN PABLO FERNANDEZ AGUILERA
TRADUCCION OFICIAL
C. IDONLIDAD 045

2002 OCT 17 A 10:13
[Signature]
JEFE DE LEGALIZACIONES
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(19) World Intellectual Property
Organization
International Bureau



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P.O. Box 6809, CH-1211 GENEVE 19, SUISSE
P.O. Box 6809, CH-1211 GENEVE 19, SUISSE

(43) International Publication Date
25 August 2005 (25.08.2005)

PCT

(10) International Publication Number
WO 2005/077943 A1

(51) International Patent Classification⁷: C07D 405/06,
319/06, 413/06, 495/04, 417/06, 407/06, A61K 31/357,
A61P 3/04, C07D 405/12

PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(21) International Application Number:
PCT/IN2005/000011

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,
SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).

(22) International Filing Date: 7 January 2005 (07.01.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
23/MUM/2004 9 January 2004 (09.01.2004) IN

Declaration under Rule 4.17:

— as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ,
CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE,
EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM,
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA,
ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ,
NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT,
BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR,
HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG)

(71) Applicant (for all designated States except US): CADILA
HEALTHCARE LIMITED [IN/IN]; Zydus Tower, Satel-
lite Cross Road, Ahmedabad 380 015, Gujarat (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): LOHRA, Braj,
Bhushan [IN/IN]; Cadila Healthcare Limited, Zydus
Tower, Satellite Cross Roads, Ahmedabad-380 015, Gu-
jarat (IN). LOHRAY, Vidya, Bhushan [IN/IN]; Cadila
Healthcare Limited, Zydus Tower, Satellite Cross Roads,
Ahmedabad-380 015, Gujarat (IN).

(74) Agents: SUBRAMANIAM, Haritharan et al.; Subrama-
niam, Nataraj & Associates, E-556, Greater Kailash II,
New Delhi - 110 048 (IN).

Published:

— with international search report
— before the expiration of the time limits for amending the
claims and to be republished in the event of receipt of
amendments

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AB, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,

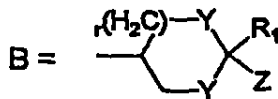
For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 2005/077943 A1

(54) Title: 1, 3 - DIOXANE DERIVATIVES AND ANALOGUES THEREOF USEFUL IN THE TREATMENT OF LA OBESITY
AND DIABETES



(I)

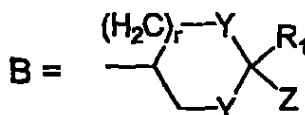
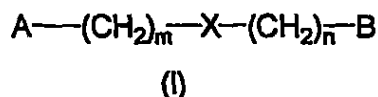


(57) Abstract: The present inven-
tion discloses novel compounds of
formula (I) and their pharmaceu-
tically useful compositions as modu-
lators of PPAR ligands

1,3-DIOXANE DERIVATIVES AND ANALOGUES THEREOF USEFUL IN THE TREATMENT OF I.A. OBESITY AND DIABETES

FIELD OF INVENTION

The present invention relates to novel compounds of the general formula (I), their
 5 tautomeric forms, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, pharmaceutical compositions containing them, use of these compounds in medicine and the intermediates involved in their preparation.



The present invention also relates to a process for the preparation of the
 10 compounds of formula (I), their tautomeric forms, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, and pharmaceutical compositions containing them.

The compounds of the general formula (I) lower blood glucose, lower or modulate triglyceride levels and/or cholesterol levels and/or low-density lipoproteins (LDL) and
 15 raises the high-density lipoproteins (HDL) plasma levels and hence are useful in combating different medical conditions, where such lowering (and raising) is beneficial. Thus, it could be used in the treatment and/or prophylaxis of obesity, hyperlipidaemia, hypercholesteremia, hypertension, atherosclerotic disease events, vascular restenosis, diabetes and many other related conditions.

20 The compounds of general formula (I) are useful to prevent or reduce the risk of developing atherosclerosis, which leads to diseases and conditions such as arteriosclerotic cardiovascular diseases, stroke, coronary heart diseases, cerebrovascular diseases, peripheral vessel diseases and related disorders.

These compounds of general formula (I) are useful for the treatment and/or
 25 prophylaxis of metabolic disorders loosely defined as Syndrome X. The characteristic features of Syndrome X include initial insulin resistance followed by hyperinsulinemia, dyslipidemia and impaired glucose tolerance. The glucose intolerance can lead to non-insulin dependent diabetes mellitus (NIDDM, Type 2 diabetes), which is characterized by hyperglycemia, which if not controlled may lead to diabetic complications or
 30 metabolic disorders caused by insulin resistance. Diabetes is no longer considered to be

associated only with glucose metabolism, but it affects anatomical and physiological parameters, the intensity of which vary depending upon stages/duration and severity of the diabetic state. The compounds of this invention are also useful in prevention, halting or slowing progression or reducing the risk of the above mentioned disorders along with the resulting secondary diseases such as cardiovascular diseases, like arteriosclerosis, atherosclerosis; diabetic retinopathy, diabetic neuropathy and renal disease including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal diseases, like microalbuminuria and albuminuria, which may be result of hyperglycemia or hyperinsulinemia.

BACKGROUND OF THE INVENTION

The present invention discloses compounds suitable for the treatment of hyperlipidemia, diabetes, obesity and similar diseases by modulating the Peroxisome Proliferator Activated Receptor (PPAR). The disease conditions, pathophysiology of the disease conditions, their effects and known & proposed therapies have been described in detail in WO 9119702, WO 9401420, WO 9413650, WO 9503038, WO 9517394, WO 9604260, WO 9604261, WO 9633998, WO 9725042, WO 9736579, WO 9828534, WO 9908501, WO 9916758, WO 9919313, WO9920614, WO 0023417, WO 0023445, WO 0023451, WO 0309841, WO 0066572, WO 0116111, WO 0116120, WO 0153257 etc. which are incorporated in their entirety as reference.

Hyperlipidemia has been recognized as the major risk factor in causing cardiovascular diseases due to atherosclerosis [*MetS Insights*, Sep; 4, 13-17 (2004)]. Atherosclerosis and other such peripheral vascular diseases affect the quality of life of a large population in the world. The therapy aims to lower the elevated plasma LDL cholesterol, low-density lipoprotein and plasma triglycerides in order to prevent or reduce the risk of occurrence of cardiovascular diseases. The detailed etiology of atherosclerosis and coronary artery diseases is discussed by Ross and Glomset [*New Engl. J. Med.*, 295, 369-377 (1976)].

Peroxisome Proliferator Activated Receptor (PPAR) is a member of the steroid/retinoid/ thyroid hormone receptor family. PPAR α , PPAR γ and PPAR δ have been identified as subtypes of PPARs. The role of PPAR, in different disease conditions is widely established PPAR γ activation has been found to play a central role in initiating and regulating adipocyte differentiation [*Endocrinology* 135, 798-800, (1994)] and

energy homeostasis, [*Cell*, 83, 803-812 (1995); *Cell*, 99, 239-242 (1999)]. PPAR α agonists would stimulate the terminal differentiation of adipocyte precursors and cause morphological and molecular changes characteristic of a more differentiated, less malignant state. During adipocyte differentiation, several highly specialized proteins are induced, which are being involved in lipid storage and metabolism. It is accepted that PPAR γ activation leads to expression of CAP gene [*Cell Biology*, 95, 14751-14756, (1998)], however, the exact link from PPAR γ activation to changes in glucose metabolism and decrease in insulin resistance in muscle has not been clear. PPAR α is involved in stimulating β -oxidation of fatty acids [*Trends Endocrine. Metabolism*, 4, 291-296 (1993)] resulting in plasma circulating free fatty acid reduction [*Current Biol.*, 5, 618-621 (1995)]. The role of PPARs in regulation of obesity-related insulin sensitivity and inflammation [*Int J Obes Relat Metab Disord*. Dec; 27 Suppl 3:S17-21(2003)], lipid metabolism and insulin sensitivity [*Diabetes* Feb;53 Suppl 1:S43-50 (2004)] have been fairly well established. PPARs are also believed to play a role in diseases associated with metabolic syndrome [*Curr Top Med Chem.*, 3(14): 1649-61(2003)]. There is growing evidence that PPAR agonists may also influence the cardiovascular system through PPAR receptors as well as directly by modulating vessel wall function [*Diabetes Metab.*, Feb; 30(1): 7-12 (2004); *Drugs Today (Barc)*, Dec;39(12):949-60 (2003)].

PPAR agonists have been found useful in the treatment of obesity [WO 97/36579; *Nat Med.*, Apr, 10(4):355-61(2004)]. Dual PPAR α and γ agonists have been suggested to be useful for Syndrome X (WO 97/25042). PPAR γ agonists and HMG-CoA reductase inhibitors have exhibited synergism and indicated the usefulness of the combination in the treatment of atherosclerosis and xanthoma [EP 0753 298; *Cardiol Rev.* May-Jun; 12(3): 158-70 (2004)].

Leptin is a protein when bound to leptin receptors is involved in sending satiety signal to the hypothalamus. Leptin resistance would therefore lead to excess food intake, reduced energy expenditure, obesity, impaired glucose tolerance and diabetes [*Science*, 269, 543-46(1995); *Recent Prog Horm Res.*, 59: 169-205 (2004); *Ann N Y Acad Sci*, Jun; 967: 363-78 (2002)]. It has been reported that insulin sensitizers lower plasma leptin concentration [*Proc. Natl. Acad. Sci.* 93, 5793-5796 (1996); WO 98/02159].

Novel heterocyclic compounds which are selective PPAR α agonists have been reported in US 2003/0166697 A1 having the general formula mentioned below which is incorporated herein as reference.

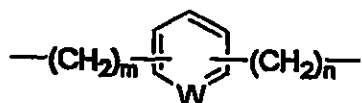
R^1 -Het-D-E

5 wherein:

R^1 is optionally substituted aryl, aromatic heterocyclic group or cycloalkyl group;

Het is an optionally substituted divalent heterocyclic group;

D is alkylene, alkenylene, alkynylene or a group of the formula

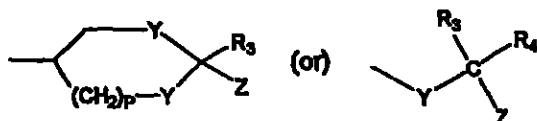


10 wherein W is CH or nitrogen;

m is 1-10;

n is 0-9, with the proviso that $m+n$ is 1-10; and

E is a group of the formula



15 wherein Y is O or S;

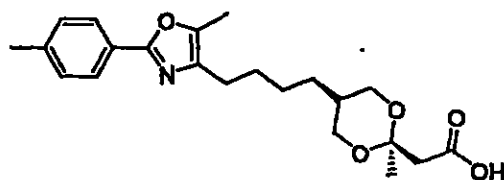
R_3 and R_4 are the same or different and each being H or alkyl;

p is 0-2;

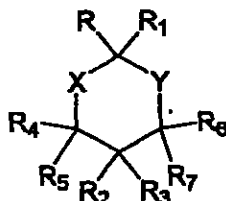
Z is carboxy, alkoxycarbonyl, hydroxymethyl, carbomoyl etc.

Representative compounds have the following structure:

20



WO 2000004011 discloses compounds having the following general formula for the treatment of dyslipidemia, atherosclerosis and diabetes;



25

where X, Y = CH₂, O, S, NRa (Ra = H, alkyl, aryl, etc.); R = H, alkyl, cycloalkyl, etc.;
R¹ = H, alkyl, hydroxyalkyl, -(CH₂)_t-COORc where t = 0-6 & Rc represents H or alkyl
group, etc.; R₂ & R₃ = H, alkyl, cycloalkyl, (C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₇)alkyl, 3-10
membered optionally substituted heterocyclic group etc.; or R₂ & R₃ optionally form a
chain -(CH₂)_{r1} (r1 = 2-5), etc.; R₄-R₇ = H, alkyl, (un)substituted aryl, etc.

However, the therapeutic potential of these compounds to treat diseases has not yet been proved and so there remains the need to develop newer medicines which are better or of comparable efficacy with the present treatment regimes, have lesser side effects and require a lower dosage regime

10 SUMMARY OF INVENTION

The objective of this invention is to develop novel compounds represented by the general formula (I) used as hypocholesterolemic, hypolipidaemic, hypolipoproteinemic, anti-obesity and antihyperglycemic agents which may have additional body weight lowering effect and beneficial effect in the treatment and/or
15 prophylaxis of diseases caused by hyperlipidaemia, diseases classified under syndrome X and atherosclerosis.

OBJECTS OF THE INVENTION

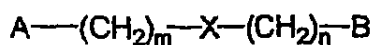
The main object of the present invention is to provide novel compounds represented by the general formula (I), their tautomeric forms, their pharmaceutically acceptable
20 salts, their pharmaceutically acceptable solvates, and pharmaceutical compositions containing them or their mixtures thereof.

Yet another object of this invention is to provide a process for the preparation of novel compounds represented by the general formula (I), their tautomeric forms, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates.

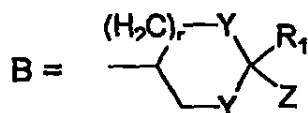
25 Still another object of the present invention is to provide pharmaceutical compositions containing compounds of the general formula (I), their tautomeric forms, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates or their mixtures in combination with suitable carriers, solvents, diluents and other media normally employed in preparing such compositions.

30 DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present invention relates to compounds of the general formula (I),



(I)



where 'A' represents optionally substituted, single or fused aryl, cycloalkyl group or an optionally substituted heteroaryl or an optionally substituted heterocyclyl group;

'm' = 0-2; 'n' = 3-6,

5 'X' represents O, S, -N-(Ra)- or -CH₂-;

Ra represents hydrogen, linear or branched, substituted or unsubstituted alkyl, acyl or aryl, aralkyl group;

'Y' at each occurrence independently represent O or S; R₁ represents H, linear or branched substituted or unsubstituted alkyl;

10 r = 0-2;

Z represents

-(CH₂)_sCOOH, alkoxycarbonyl, hydroxymethyl, -CN, substituted or unsubstituted tetrazoles, alkylcarbonyl groups, s = 0-4;

When 'A' is substituted, suitable substitutions on 'A' may be selected from
 15 hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from amidino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino,
 20 carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkylsulfonylamino, alkylsulfonyloxy, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkoxyamino, hydroxyl amino, sulfenyl derivatives, sulfonyl
 25 derivatives,

with the proviso that when X = CH₂ and

i) 'A' represents substituted heterocyclic group, the substitutions on 'A' does not represent aryl, aromatic, heterocyclic or cycloalkyl group; and

- ii) 'A' represents substituted aryl group, the substituent on 'A' represents alkylsulfonyloxy, aryloxy, aralkoxy, cycloalkyl, heteroaryl or heterocyclic group.

Suitable substitutions on 'B' may be selected from hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from alkyl, haloalkyl, aryl groups.

Suitable substitutions on any of the substituents on 'A' & 'B' may be selected from hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from amidino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkoxyamino, hydroxyl amino groups.

The term "substituted" used alone or in combination with other radicals, denotes suitable substituents on that radical such as substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted aryl, etc, mentioned anywhere in the specification. The suitable substituents include, but are not limited to the following radicals, alone or in combination with other radicals, such as, hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, amidino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, sulfonic acid and its derivatives.

The various groups, radicals and substituents used anywhere in the specification are described in the following paragraphs.

The term "alkyl" used herein, either alone or in combination with other radicals, denotes a linear or branched radical containing one to twelve carbons, such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, amyl, *t*-amyl, *n*-pentyl, *n*-hexyl, *iso*-hexyl, heptyl, octyl and the like.

The term "alkenyl" used herein, either alone or in combination with other radicals, denotes a linear or branched radical containing two to twelve carbons such as vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl and the like. The term "alkenyl" includes dienes and trienes of straight and branched chains.

The term "alkynyl" used herein, either alone or in combination with other radicals, denotes a linear or branched radical containing two to twelve carbons, such as ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, and the like. The term "alkynyl" includes di- and tri-ynes.

The term "cycloalkyl" used herein, either alone or in combination with other radicals, denotes a radical containing three to seven carbons, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

The term "cycloalkenyl" used herein, either alone or in combination with other radicals, denotes a radical containing three to seven carbons, such as cyclopropenyl, 1-cyclobutenyl, 2-cyclobutenyl, 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, cycloheptadienyl, cycloheptatrienyl, and the like.

The term "alkoxy" used herein, either alone or in combination with other radicals, denotes an alkyl radical, as defined above, attached directly to an oxygen atom, such as methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, *iso*-butoxy, pentyloxy, hexyloxy, and the like.

The term "alkenoxy" used herein, either alone or in combination with other radicals, denotes an alkenyl radical, as defined above, attached to an oxygen atom, such as vinyloxy, allyloxy, butenoxy, pentenoxy, hexenoxy, and the like.

The term "cycloalkoxy" used herein, either alone or in combination with other radicals, denotes a cycloalkyl radical as defined above, attached directly to an oxygen atom, such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like.

The term "halo" or "halogen" used herein, either alone or in combination with other radicals, such as "haloalkyl", "perhaloalkyl" etc refers to a fluoro, chloro, bromo or iodo group. The term "haloalkyl" denotes a alkyl radical, as defined above, substituted with one or more halogens; such as perhaloalkyl, more preferably,

perfluoro(C₁-C₆)alkyl such as fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, trifluoroethyl, mono or polyhalo substituted methyl, ethyl, propyl, butyl, pentyl or hexyl groups. The term "haloalkoxy" denotes a haloalkyl, as defined above, directly attached to an oxygen atom, such as fluoromethoxy, chloromethoxy, fluoroethoxy chloroethoxy groups, and the like. The term
5 "perhaloalkoxy" denotes a perhaloalkyl radical, as defined above, directly attached to an oxygen atom, trifluoromethoxy, trifluoroethoxy, and the like.

The term "aryl" or "aromatic" used herein, either alone or in combination with other radicals, denotes an aromatic system containing one, two or three rings wherein
10 such rings may be attached together in a pendant manner or may be fused, such as phenyl, naphthyl, tetrahydronaphthyl, indane, biphenyl, and the like. The term "aralkyl" denotes an alkyl group, as defined above, attached to an aryl, such as benzyl, phenethyl, naphthylmethyl, and the like. The term "aryloxy" denotes an aryl radical, as defined above, attached to an alkoxy group, such as phenoxy, naphthyloxy and the like, which
15 may be substituted. The term "aralkoxy" denotes an arylalkyl moiety, as defined above, such as benzyloxy, phenethyloxy, naphthylmethyloxy, phenylpropyloxy, and the like, which may be substituted.

The term "heterocyclyl" or "heterocyclic" used herein, either alone or in combination with other radicals, denotes saturated, partially saturated and unsaturated
20 ring-shaped radicals, the heteroatoms selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include aziridiny, azetidiny, pyrrolidiny, imidazolidiny, piperidiny, piperaziny, 2-oxopiperidiny, 4-oxopiperidiny, 2-oxopiperaziny, 3-oxopiperaziny, morpholiny, thiomorpholiny, 2-oxomorpholiny, azepiny, diazepiny, oxapiny, thiazepiny, oxazolidiny, thiazolidiny, and the like;
25 examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, and the like.

The term "heteroaryl" or "heteroaromatic" used herein, either alone or in combination with other radicals, denotes unsaturated 5 to 6 membered heterocyclic radicals containing one or more hetero atoms selected from O, N or S, such as pyridyl,
30 thienyl, furyl, pyrrolyl, oxazoly, thiazoly, isothiazoly, imidazoly, isoxazoly, oxadiazoly, thiadiazoly, triazoly, tetrazoly, benzopyrany, benzopyranonyl, benzofurany, benzothienyl, indoliny, indolyl, azaindoly, azaindoliny, benzodihydrofurany, benzodihydrothienyl, pyrazolopyrimidiny, pyrazolopyrimidonyl, azaquinazolinyl, azaquinazolinoyl, pyridofurany, pyridothienyl, thienopyrimidyl,

thienopyrimidonyl, quinolinyl, pyrimidinyl, pyrazolyl, quinazolinyl, quinazolonyl, pyrimidonyl, pyridazinyl, triazinyl, benzoxazinyl, benzoxazinonyl, benzothiazinyl, benzothiazinonyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzotriazolyl, phthalazynil, naphthylidinyl, purinyl, carbazolyl, phenothiazinyl, phenoxazinyl, and the
5 like.

The term "acyl" used herein, either alone or in combination with other radicals, denotes a radical containing one to eight carbons such as formyl, acetyl, propanoyl, butanoyl, *iso*-butanoyl, pentanoyl, hexanoyl, heptanoyl, benzoyl and the like, which may be substituted.

10 The term "acyloxy" used herein, either alone or in combination with other radicals, denotes a radical acyl, as defined above, directly attached to an oxygen atom, such as acetyloxy, propionyloxy, butanoyloxy, *iso*-butanoyloxy, benzoyloxy and the like.

The term "acylamino" used herein, either alone or in combination with other
15 radicals, denotes an acyl group as defined earlier, may be CH_3CONH , $\text{C}_2\text{H}_5\text{CONH}$, $\text{C}_3\text{H}_7\text{CONH}$, $\text{C}_4\text{H}_9\text{CONH}$, $\text{C}_6\text{H}_5\text{CONH}$ and the like, which may be substituted.

The term "mono-substituted amino" used herein, either alone or in combination with other radicals, denotes an amino group, substituted with one group selected from $(\text{C}_1\text{-C}_6)\text{alkyl}$, substituted alkyl, aryl, substituted aryl or arylalkyl groups. Examples of
20 monoalkylamino group include methylamine, ethylamine, *n*-propylamine, *n*-butylamine, *n*-pentylamine and the like.

The term "disubstituted amino" used herein, either alone or in combination with other radicals, denotes an amino group, substituted with two radicals that may be same or different selected from $(\text{C}_1\text{-C}_6)\text{alkyl}$, substituted alkyl, aryl, substituted aryl, or
25 arylalkyl groups, such as dimethylamino, methylethylamino, diethylamino, phenylmethyl amino and the like.

The term "arylamino" used herein, either alone or in combination with other radicals, denotes an aryl group, as defined above, linked through amino having a free valence bond from the nitrogen atom, such as phenylamino, naphthylamino, *N*-methyl
30 anilino and the like.

The term "aralkylamino" used herein, either alone or in combination with other radicals, denotes an arylalkyl group as defined above linked through amino having a free valence bond from the nitrogen atom e.g. benzylamino, phenethylamino, 3-phenylpropylamino, 1-naphthylmethylamino, 2-(1-naphthyl)ethylamino and the like.

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The term "oxo" or "carbonyl" used herein, either alone ($-C=O-$) or in combination with other radicals, such as "alkylcarbonyl", denotes a carbonyl radical ($-C=O-$) substituted with an alkyl radical such as acyl or alkanoyl, as described above.

The term "carboxylic acid" used herein, alone or in combination with other radicals, denotes a $-COOH$ group, and includes derivatives of carboxylic acid such as esters and amides. The term "ester" used herein, alone or in combination with other radicals, denotes $-COO-$ group, and includes carboxylic acid derivatives, where the ester moieties are alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, and the like, which may be substituted; aryloxy carbonyl group such as phenoxycarbonyl, naphthyloxy carbonyl, and the like, which may be substituted; aralkoxycarbonyl group such as benzyloxy carbonyl, phenethyloxy carbonyl, naphthylmethoxycarbonyl, and the like, which may be substituted;

The term "amide" used herein, alone or in combination with other radicals, represents an aminocarbonyl radical ($H_2N-C=O-$), wherein the amino group is mono- or di-substituted or unsubstituted, such as methylamide, dimethylamide, ethylamide, diethylamide, and the like. The term "aminocarbonyl" used herein, either alone or in combination with other radicals, with other terms such as 'aminocarbonylalkyl', "n-alkylaminocarbonyl", "N-arylaminocarbonyl", "N,N-dialkylaminocarbonyl", "N-alkyl-N-arylaminocarbonyl", "N-alkyl-N-hydroxyaminocarbonyl", and "N-alkyl-N-hydroxyaminocarbonylalkyl", substituted or unsubstituted. The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denotes aminocarbonyl radicals, as defined above, which have been substituted with one alkyl radical and with two alkyl radicals, respectively. Preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to aminocarbonyl radical. The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl, and one aryl radical. The term "aminocarbonylalkyl" includes alkyl radicals substituted with aminocarbonyl radicals.

The term "hydroxyalkyl" used herein, either alone or in combination with other radicals, denotes an alkyl group, as defined above, substituted with one or more hydroxy radicals, such as hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl and the like.

The term "aminoalkyl" used herein, alone or in combination with other radicals, denotes an amino ($-NH_2$) moiety attached to an alkyl radical, as defined above, which

may be substituted, such as mono- and di-substituted aminoalkyl. The term "alkylamino" used herein, alone or in combination with other radicals, denotes an alkyl radical, as defined above, attached to an amino group, which may be substituted, such as mono- and di-substituted alkylamino.

5 The term "alkoxyalkyl" used herein, alone or in combination with other radicals, denotes an alkoxy group, as defined above, attached to an alkyl group, such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like. The term "aryloxyalkyl" used herein, alone or in combination with other radicals, includes phenoxymethyl, naphthyloxymethyl, and the like. The term "aralkoxyalkyl" used
10 herein, alone or in combination with other radicals, includes $C_6H_5CH_2OCH_2$, $C_6H_5CH_2OCH_2CH_2$, and the like.

The term "alkylthio" used herein, either alone or in combination with other radicals, denotes a straight or branched or cyclic monovalent substituent comprising an alkyl group of one to twelve carbon atoms, as defined above, linked through a divalent
15 sulfur atom having a free valence bond from the sulfur atom, such as methylthio, ethylthio, propylthio, butylthio, pentylthio and the like. Examples of cyclic alkylthio are cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio and the like, which may be substituted.

The term "thioalkyl" used herein, either alone or in combination with other
20 radicals, denotes an alkyl group, as defined above, attached to a group of formula $-SR'$, where R' represents hydrogen, alkyl or aryl group, e.g. thiomethyl, methylthiomethyl, phenylthiomethyl and the like, which may be substituted.

The term "arylthio" used herein, either alone or in combination with other radicals, denotes an aryl group, as defined above, linked through a divalent sulfur atom,
25 having a free valence bond from the sulfur atom such as phenylthio, naphthylthio and the like.

The term "alkoxycarbonylamino" used herein, alone or in combination with other radicals, denotes an alkoxycarbonyl group, as defined above, attached to an amino group, such as methoxycarbonylamino, ethoxycarbonylamino, and the like. The
30 term "aryloxy carbonylamino" used herein, alone or in combination with other radicals, denotes an aryloxy carbonyl group, as defined above, attached to the an amino group, such as C_6H_5OCONH , $C_6H_5OCONCH_3$, $C_6H_5OCONC_2H_5$, $C_6H_4(CH_3O)CONH$, $C_6H_4(OCH_3)OCONH$, and the like. The term "aralkoxycarbonylamino" used herein, alone or in combination with other radicals, denotes an aralkoxycarbonyl group, as

defined above, attached to an amino group $C_6H_5CH_2OCONH$, $C_6H_5CH_2CH_2CH_2OCONH$, $C_6H_5CH_2OCONHCH_3$, $C_6H_5CH_2OCONC_2H_5$, $C_6H_4(CH_3)CH_2OCONH$, $C_6H_4(OCH_3)CH_2OCONH$, and the like.

The term "aminocarbonylamino", "alkylaminocarbonylamino",
 5 "dialkylaminocarbonylamino" used herein, alone or in combination with other radicals, denotes a carbonylamino ($-CONH_2$) group, attached to amino(NH_2), alkylamino group or dialkylamino group respectively, where alkyl group is as defined above.

The term "amidino" used herein, either alone or in combination with other radicals, denotes a $-C(=NH)-NH_2$ radical. The term "alkylamidino" denotes an alkyl
 10 radical, as discussed above, attached to an amidino group.

The term "alkoxyamino" used herein, alone or in combination with other radicals, denotes an alkoxy group, as defined above, attached to an amino group. The term "hydroxyamino" used herein, alone or in combination with other radicals, denotes $-NHOH$ moiety, and may be substituted.

15 The term "sulfenyl" or "sulfenyl and its derivatives" used herein, alone or in combination with other radicals, denotes a bivalent group, $-SO-$ or R_xSO , where R_x is substituted or unsubstituted alkyl, aryl, heteroaryl, heterocyclyl, and the like.

The term "sulfonyl" or "sulfones and its derivatives" used herein, either alone or in combination with other radicals, with other terms such as alkylsulfonyl, denotes
 20 divalent radical $-SO_2-$, or R_xSO_2- , where R_x is substituted or unsubstituted groups selected from alkyl, aryl, heteroaryl, heterocyclyl, and the like. "Alkylsulfonyl" denotes alkyl radicals, as defined above, attached to a sulfonyl radical, such as methylsulfonyl, ethylsulfonyl, propylsulfonyl and the like. The term "arylsulfonyl" used herein, either alone or in combination with other radicals, denotes aryl radicals, as defined above,
 25 attached to a sulfonyl radical, such as phenylsulfonyl and the like.

Suitable groups and substituents on the groups may be selected from those described anywhere in the specification.

Particularly useful compounds may be selected from
 Methyl-5-[4-(2-ethyl-4-oxo-4H-quinazolin-3-yl)-butyl]-2-methyl-[1,3]dioxane-2-
 30 carboxylate;
 Methyl-5-[4-(2-ethyl-quinazolin-4-yloxy)-butyl]-2-methyl-[1,3]dioxane-2-carboxylate;
 Methyl-5-[6-(4-chloro-phenyl)-5-(4-methylsulfanyl-phenyl)-6-oxo-hexyl]-2-methyl-
 [1,3]dioxane-2-carboxylate;

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- Methyl-5-[4-(2,3-dihydro-benzo[1,4]oxazin-4-yl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylate;
- Methyl-2-methyl-5-(4-phenoxazin-10-yl-butyl)-[1,3]dioxane-2-carboxylate;
- Methyl-5-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylate;
- 5 Methyl-5-(4-carbazol-9-yl-butyl)-2-methyl-[1,3]dioxane-2-carboxylate;
- Methyl-2-methyl-5-[4-(3-oxo-2,3-dihydro-benzo[1,4]thiazin-4-yl)-butyl]-[1,3]dioxane-2-carboxylate;
- Methyl-5-[4-(2,3-dihydro-benzo[1,4]thiazin-4-yl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylate;
- 10 Methyl-2-methyl-5-(4-pheno-thiazin-10-yl-butyl)-[1,3]dioxane-2-carboxylate;
- Methyl-5-(4-indol-1-yl-butyl)-2-methyl-[1,3]dioxane-2-carboxylate;
- Methyl-2-methyl-5-(5-phenyl-5-pyridin-4-yl-pentyl)-[1,3]dioxane-2-carboxylate;
- Methyl-5-[4-(4-benzyl-phenoxy)-butyl]-2-methyl-[1,3]dioxane-2-carboxylate;
- 15 Methyl-2-methyl-5-[4-(3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-butyl]-[1,3]dioxane-2-carboxylate;
- Methyl-5-[4-[2-(2-hydroxy-ethyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl]-butyl]-2-methyl-[1,3]dioxane-2-carboxylate;
- Methyl-2-methyl-5-[4-(4-phenoxy-phenoxy)-butyl]-[1,3]dioxane-2-carboxylate;
- 20 Methyl-5-(3-benzo[1,3]dioxol-5-yl-propyl)-2-methyl-[1,3]dioxane-2-carboxylate;
- Methyl-5-[4-(4-methanesulfonyloxy-phenyl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylate;
- Methyl-5-[4-(4-benzyloxy-phenyl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylate;
- Methyl-2-methyl-5-(3-phenylsulfanyl-propyl)-[1,3]dioxane-2-carboxylate;
- 25 Ethyl-5-[3-(4-bromo-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylate;
- Methyl-2-methyl-5-[3-(4-phenoxy-phenoxy)-propyl]-[1,3]dioxane-2-carboxylate;
- Methyl-5-[3-(4-isopropyl-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylate;
- Methyl-2-methyl-5-(3-p-tolyloxy-propyl)-[1,3]dioxane-2-carboxylate;
- Methyl-5-[3-(4-bromo-phenylsulfanyl)-propyl]-2-methyl-[1,3]dioxane-2-carboxylate;
- 30 Methyl-2-methyl-5-(3-phenoxy-propyl)-[1,3]dioxane-2-carboxylate;
- Methyl-5-[3-(4-fluoro-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylate;
- Methyl-2-methyl-5-[3-(naphthalen-2-yloxy)-propyl]-[1,3]dioxane-2-carboxylate;
- Methyl-5-[3-(4-benzyloxy-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylate;
- Methyl-5-[3-(4-methoxy-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylate;

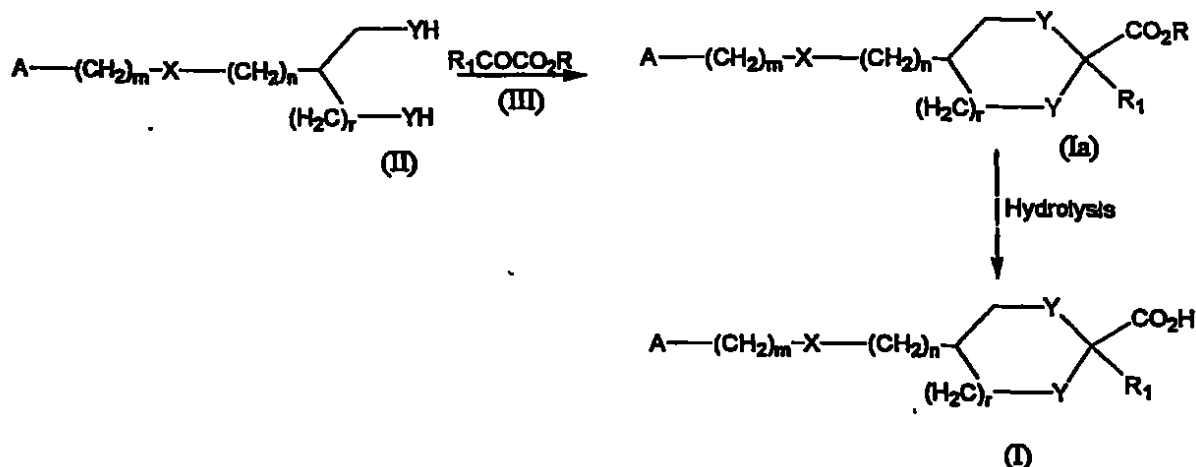
- Methyl-5-[3-(4-benzyl-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylate;
5-[4-(2-Ethyl-4-oxo-4H-quinazolin-3-yl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylic
acid and its pharmaceutically acceptable salts;
5-[4-(2-Ethyl-quinazolin-4-yloxy)-butyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and
5 its pharmaceutically acceptable salts;
5-[5-(4-Chloro-phenyl)-5-(4-methylsulfanyl-phenyl)-6-oxo-hexyl]-2-methyl-
[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
5-[4-(2,3-Dihydro-benzo[1,4]oxazin-4-yl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylic
acid and its pharmaceutically acceptable salts;
10 2-Methyl-5-(4-phenoxazin-10-yl-butyl)-[1,3]dioxane-2-carboxylic acid and its
pharmaceutically acceptable salts;
5-(4-Carbazol-9-yl-butyl)-2-methyl-[1,3]dioxane-2-carboxylic acid and its
pharmaceutically acceptable salts;
2-Methyl-5-[4-(3-oxo-2,3-dihydro-benzo[1,4]thiazin-4-yl)-butyl]-[1,3]dioxane-2-
15 carboxylic acid and its pharmaceutically acceptable salts;
5-[4-(2,3-Dihydro-benzo[1,4]thiazin-4-yl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylic
acid and its pharmaceutically acceptable salts;
2-Methyl-5-(4-phenothiazin-10-yl-butyl)-[1,3]dioxane-2-carboxylic acid and its
pharmaceutically acceptable salts;
20 5-(4-Indol-1-yl-butyl)-2-methyl-[1,3]dioxane-2-carboxylic acid and its
pharmaceutically acceptable salts;
2-Methyl-5-(5-phenyl-5-pyridin-4-yl-pentyl)-[1,3]dioxane-2-carboxylic acid and its
pharmaceutically acceptable salts;
5-[4-(4-Benzyl-phenoxy)-butyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its
25 pharmaceutically acceptable salts;
2-Methyl-5-[4-(3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-butyl]-[1,3]dioxane-2-
carboxylic acid and its pharmaceutically acceptable salts;
5-[4-[2-(2-Hydroxy-ethyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl]-butyl]-2-methyl-
[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
30 2-Methyl-5-[4-(4-phenoxy-phenoxy)-butyl]-[1,3]dioxane-2-carboxylic acid and its
pharmaceutically acceptable salts;
5-(3-Benzo[1,3]dioxol-5-yl-propyl)-2-methyl-[1,3]dioxane-2-carboxylic acid and its
pharmaceutically acceptable salts;

- 5-[4-(4-Methanesulfonyloxy-phenyl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 5-[4-(4-Benzoyloxy-phenyl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 5 2-Methyl-5-(3-phenylsulfanyl-propyl)-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 5-[3-(4-Bromo-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 2-Methyl-5-[3-(4-phenoxy-phenoxy)-propyl]-[1,3]dioxane-2-carboxylic acid and its
- 10 pharmaceutically acceptable salts;
- 5-[3-(4-Isopropyl-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 2-Methyl-5-(3-p-tolyloxy-propyl)-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 15 5-[3-(4-Bromo-phenylsulfanyl)-propyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 2-Methyl-5-(3-phenoxy-propyl)-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 5-[3-(4-Fluoro-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its
- 20 pharmaceutically acceptable salts;
- 2-Methyl-5-[3-(naphthalen-2-yloxy)-propyl]-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 5-[3-(4-Benzoyloxy-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 25 5-[3-(4-Methoxy-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 5-[3-(4-Benzyl-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;

The novel compounds of this invention may be prepared using the reactions and

30 techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. It is understood by those skilled in the art that the nature and order of the synthetic steps presented may be varied for the purpose of optimizing the formation of the compounds of the present invention.

Scheme 1



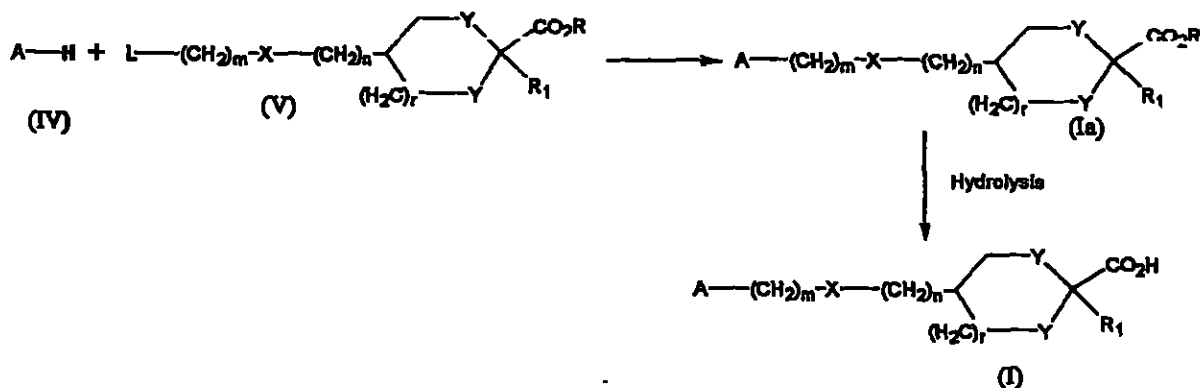
The compounds of general formula (I) wherein all the symbols are as defined earlier, may be prepared by route outlined in scheme 1 above which comprises

- i) Reacting a compound of formula (II) with a compound of formula (III) to obtain compound of formula (Ia) wherein R represents alkyl group and all other symbols are as defined earlier. Generally, the reaction may be carried out in an appropriate solvent selected from polar solvents such as acetonitrile, DMF and the like, ether solvents such as THF, dioxane, diethyl ether, dimethoxy ethane and the like, halogenated solvents like $CHCl_3$ or dichloromethane, dichloroethane and the like, hydrocarbon solvents such as benzene, toluene, n-hexane, cyclohexane and the like, ester solvents such as methyl acetate, ethyl acetate, isopropyl acetate and the like or mixtures thereof, in the presence of Lewis acid such as boron trifluoride diethyl ether complex at -22 to 120 °C. The reaction may be carried out in the atmosphere of an inert gas such as nitrogen. The reaction time may vary from 30 minutes to 24 hours.
- ii) Hydrolyzing a compound of formula (Ia) with suitable reagents/solvents to a compound of formula (I) wherein all the symbols are as defined earlier. Suitable hydrolyzing solvents may be selected from alcoholic solvents like methanol, ethanol, propanol, isopropanol, *t*-butanol and the like or mixtures thereof, and water in the presence of suitable acids or bases at -20 to 100 °C. Suitable acids may be HCl, PTSA and the like; suitable bases may be LiOH, NaOH, KOH and the like.

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- iii) optionally, if desired, the compounds of formula (I) are converted to their suitable pharmaceutically acceptable salts by techniques known in the art.

Scheme 2:



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Alternatively, the compounds of general formula (I) wherein all the symbols are as defined earlier may be prepared by route outlined in scheme 2 above which comprises;

- i) Reacting the compound of general formula (V) where L represents a suitable leaving group such as halogen, mesylate, tosylate, triflate & the like, with compounds of general formula (IV) to obtain the compound of general formula (Ia). Suitable bases like metal hydrides e.g. NaH and the like, alkali metal carbonates e.g. potassium carbonate, sodium carbonate and the like, sodium hydroxide, potassium hydroxide, organic bases e.g. trialkyl amines and the like, organolithium reagents e.g. butyllithium, lithium diisopropylamide, lithium hexamethyldisilazide and the like may be used. Reaction may be carried out in suitable solvents like DMF, DMSO, THF, dioxane, n-hexane, cyclohexane, dichloroethane, acetone, dichloromethane, toluene and the like or mixture thereof based on the suitability for the bases used. Reaction temperature may range from $-78^{\circ}C$ to the reflux temperature of the solvent(s) used. Inert atmosphere may optionally be maintained using N_2 , He, or argon gas. Reaction time may range from 1 to 72 hours.
- ii) Hydrolyzing a compound of formula (Ia) with suitable reagents/solvents to a compound of formula (I) wherein all the symbols are as defined earlier. Suitable hydrolyzing solvents may be selected from alcoholic solvents like methanol, ethanol, propanol, isopropanol, *t*-butanol and the like or mixtures thereof, and

25

water in the presence of suitable acids or bases at -20 to 100 °C. Suitable acids may be HCl, PTSA and the like; suitable bases may be NaOH, KOH and the like.

- iii) optionally, if desired, the compounds of formula (I) are converted to their
5 suitable pharmaceutically acceptable salts by techniques known in the art.

It will be appreciated that in any of the above mentioned reactions any reactive group in the substrate molecule may be protected, according to conventional chemical practice. Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. The methods of formation and removal in such
10 protecting groups are those conventional methods appropriate to the molecule being protected. T. W. Greene and P. G. M. Wuts "Protective groups in Organic Synthesis", John Wiley & Sons, Inc, 1999, 3rd Ed., along with references therein.

It will be appreciated that when substituents have different sites where they can be attached, such differently attached substituents are also included in the present
15 invention.

The novel compounds of the present invention can be formulated into suitable pharmaceutically acceptable compositions by combining with suitable excipients by techniques and processes and concentrations as are well known.

The compounds of formula (I) or pharmaceutical compositions containing them may
20 be administered either by oral, topical or parenteral administration.

The pharmaceutical composition is provided by employing conventional techniques. Preferably the composition is in unit dosage form containing an effective amount of the active component, that is, the compounds of formula (I) according to this invention.

The quantity of active component, that is, the compounds of formula (I)
25 according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application method, the potency of the particular compound and the desired concentration. Generally, the quantity of active component will range between 0.5 % to 90 % by weight of the composition.

30 The compounds of general formula (I) or the compositions thereof are useful for the treatment and/or prophylaxis of disease caused by metabolic disorders such as hyperlipidemia, insulin resistance, leptin resistance, Syndrome X, hyperglycemia, obesity, or inflammation.

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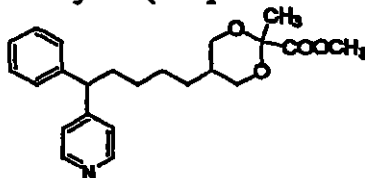
The invention is explained in greater detail by the examples given below, which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

It will be appreciated that one or more of the processes described in the general schemes above may be used to prepare the compounds of the present invention.

¹H NMR spectral data given in the tables (vide infra) are recorded using a 300 MHz spectrometer (Bruker AVANCE-300) and reported in δ scale. Until and otherwise mentioned the solvent used for NMR is CDCl₃ using Tetramethyl silane as the internal standard.

Preparation 1

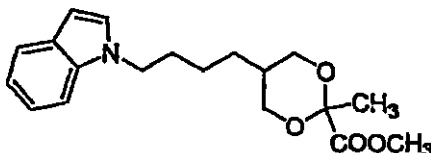
Methyl-2-methyl-5-(5-phenyl-5-pyridin-4-yl-pentyl)-[1,3]dioxane-2-carboxylate.(compound No.12)



A solution of 4-benzyl pyridine (250 mg) in dry tetrahydrofuran (3 mL) was cooled to -78 °C and 2.35 mL of 1M solution of lithium hexamethyldisilazide in tetrahydrofuran was added. After stirring for one hour at the same temperature another solution of Methyl-5-(4-iodo-butyl)-2-methyl-[1,3]dioxane-2-carboxylate (500 mg) in tetrahydrofuran (3 mL) was added and the reaction mixture was stirred for 3 hours allowing the temperature to rise to 30 °C. The reaction mixture was poured in to ice cold water (25 mL) and extracted with ethyl acetate (3 X 10 mL). The combined organic extract was washed with water (25 mL), brine solution (25 mL), dried over sodium sulfate and evaporated under reduced pressure. The crude product obtained was flash chromatographed over silicagel using 10 % ethyl acetate in petroleum ether as eluent to yield 233 mg of the product.

Preparation 2

Methyl-5-(4-indol-1-yl-butyl)-2-methyl-[1,3]dioxane-2-carboxylate (compound No.11)

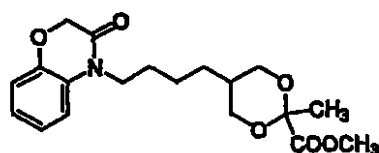


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A solution of indole (340 mg) in dimethyl sulfoxide (3 mL) was added to an ice cold suspension of potassium hydroxide (326 mg) in dimethyl sulfoxide (3 mL). After stirring for 10 minutes a solution of methyl-5-(4-iodo-butyl)-2-methyl-[1,3]dioxane-2-carboxylate (1.0 g) in dimethyl sulfoxide (5 mL) was added and the reaction mixture was stirred for 5 hours at 30 °C. Reaction mixture was poured in to ice cold water (50 mL) and extracted with ethyl acetate (3 X 20 mL). The combined organic extract was washed with water (50 mL), brine solution (50 mL), dried over sodium sulfate and evaporated under reduced pressure. Crude product was flash chromatographed over silica gel using 10 % ethyl acetate in petroleum ether as eluent to yield 400 mg of product.

Preparation 3

Methyl-2-methyl-5-[4-(3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-butyl]-[1,3]dioxane-2-carboxylate (compound No.14)



15

To a stirred suspension of cesium carbonate (1.0 g) in dimethyl formamide (5 mL) was added a solution of 4H-benzo[1,4]oxazin-3-one (250 mg) in dimethyl formamide (3 mL) was added. After stirring in nitrogen atmosphere for 30 minutes another solution of Methyl-5-(4-iodo-butyl)-2-methyl-[1,3]dioxane-2-carboxylate (574 mg) in dimethyl formamide (3 mL) was added and the reaction mixture was stirred at ambient temperature for 2 hours. Reaction mixture was poured into ice cold water (50 mL) and extracted with ethyl acetate (3 X 30 mL). The combined organic extract was washed with water (50 mL), brine solution (50 mL), dried over sodium sulfate and evaporated under reduced pressure. Crude product was flash chromatographed over silica gel using 15 % ethyl acetate in petroleum ether as eluent to yield 483 mg of product.

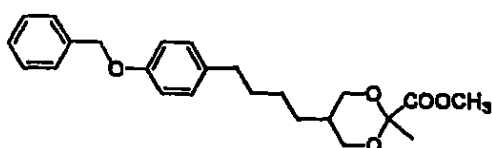
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Preparation 4

Methyl 5-[4-(4-benzyloxy-phenyl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylate (compound No.18)

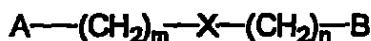
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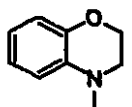
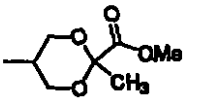
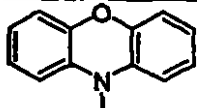
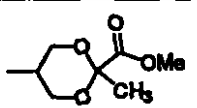
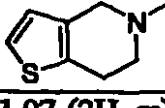
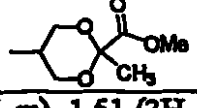
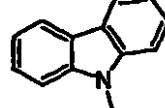
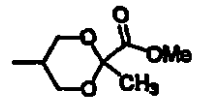
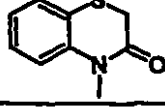
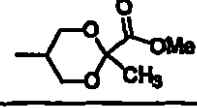
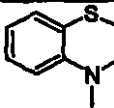
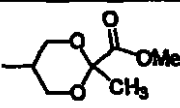
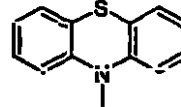
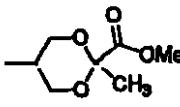
To a solution of 2-[4-(4-benzyloxy-phenyl)-butyl]-propane-1,3-diol (1.5 g) in acetonitrile (15 mL) was added methyl pyruvate (2.1 g) followed by 98 % boron trifluoride-diethyl ether complex (1.7 g) and the reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was poured into a saturated solution of sodium bicarbonate (100 mL) and extracted with ethyl acetate (3 X 50 mL). The combined organic extract was washed with water (100 mL), brine solution (100 mL), dried over sodium sulfate and evaporated under reduced pressure. Crude product was flash chromatographed over silica gel using 10 % ethyl acetate in petroleum ether as solvent to obtain 867 mg of title product.

Table 1:

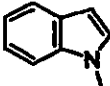
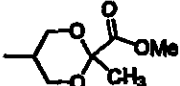
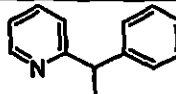
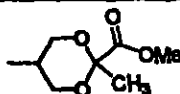
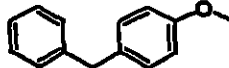
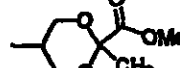
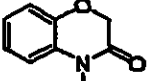
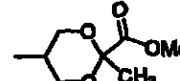
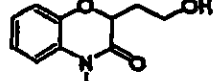
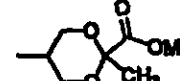
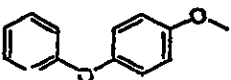
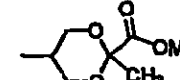
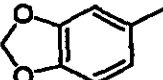


S.No.	A	B	$-(CH_2)_m-X-(CH_2)_n-$	Mol. Wt.	% Yield
1.			$(CH_2)_4$	388	60
	¹ H: 1.1 (2H, m), 1.2 (2H, m), 1.4 (3H, t, J=7.3 Hz), 1.5 (3H, s), 1.7 (2H, m), 2.0 (1H, m), 2.8 (2H, q, J=7.3 Hz), 3.4 (2H, t, J=11.5 Hz), 3.8 (3H, s), 4.0 (2H, dd, J=11.8&4.5 Hz), 4.06 (2H, t, J=7.7 Hz), 7.4 (1H, t, J=7.6 Hz), 7.6 (1H, d, J=7.7 Hz), 7.7 (1H, t, J=7.0 Hz), 8.2 (1H, d, J=7.8 Hz).				
2.			$(CH_2)_4$	388	40
	¹ H: 1.1 (2H, m), 1.2 (2H, m), 1.4 (3H, t, J=7.6 Hz), 1.5 (3H, s), 1.8 (2H, m), 2.0 (1H, m), 2.9 (2H, q, J=7.6 Hz), 3.4 (2H, t, J=11.5 Hz), 3.8 (3H, s), 4.0 (2H, dd, J=11.9 & 4.5 Hz), 4.5 (2H, t, J=6.5 Hz), 7.5 (1H, t, J=7.2 Hz), 7.8 (1H, t, J=7.1 Hz), 7.8 (1H, d, J=8.3 Hz), 8.1 (1H, d, J=8.0 Hz).				
3.			$(CH_2)_4$	490.5	48
	¹ H: 1.0 (2H, m), 1.2 (2H, m), 1.49 (3H, s), 1.7 (2H, m), 1.9 (1H, m), 2.0 (2H, m), 2.4 (3H, s), 3.3 (2H, t, J=11.6 Hz), 3.8 (2H, s), 3.9 (2H, dd, J=11.9 & 4.56 Hz), 4.3 (1H, t, J=7.17 Hz), 7.1 (4H, m), 7.3 (2H, d, J=8.5 Hz), 7.8 (2H, d, J=8.5 Hz).				

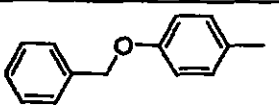
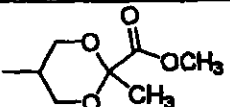
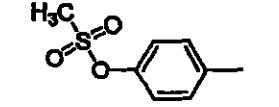
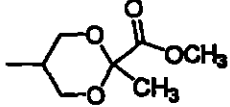
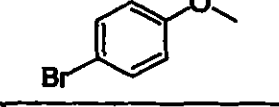
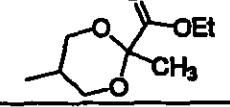
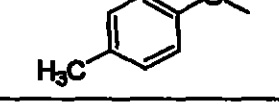
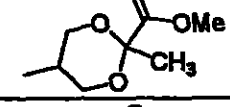
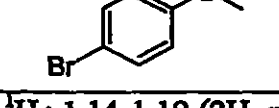
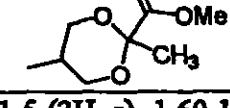
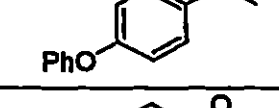
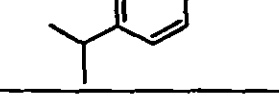
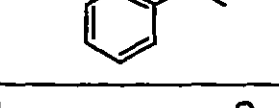
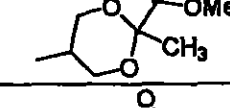
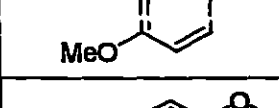
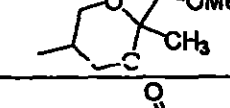
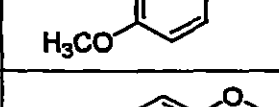
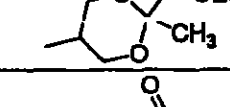
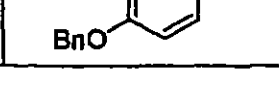
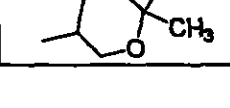
32

4.			(CH ₂) ₄	349	54
	¹ H: 1.08 (2H, m), 1.3 (2H, m), 1.58 (3H, s), 1.75 (2H, m), 2.0 (2H, m), 3.2 (2H, t, J=7.5 Hz), 3.3 (2H, m), 3.4 (2H, t, J=11.6 Hz), 3.83 (3H, s), 3.96 (2H, dd, J=4.6 & 11.8 Hz), 4.22 (2H, t, J=4.3 Hz), 6.6 (2H, m), 6.8 (2H, m).				
5.			(CH ₂) ₄	397	29
	¹ H: 1.08 (2H, m), 1.36 (2H, m), 1.51 (3H, s), 1.65 (2H, m), 2.0 (2H, m), 3.4 (4H, m), 3.83 (3H, s), 3.9 (2H, dd, J=4.6 & 11.6 Hz), 6.4 (2H, d, J=7.86 Hz), 6.62 (4H, m), 6.77 (2H, m).				
6.			(CH ₂) ₄	353	77
	¹ H: 1.07 (2H, m), 1.3 (2H, m), 1.51 (3H, s), 1.6 (2H, m), 2.03 (1H, m), 2.5 (2H, d, J=7.8 Hz), 2.76 (2H, t, J=5.0 Hz), 2.8 (2H, m), 3.39 (2H, t, J=11.64 Hz), 3.54 (2H, s), 3.53 (3H, s), 3.95 (2H, m), 6.7 (1H, d, J=5.0 Hz), 7.0 (1H, d, J=5.0 Hz).				
7.			(CH ₂) ₄	381	86
	¹ H: 1.0 (2H, m), 1.3 (2H, m), 1.49 (3H, s), 1.87 (2H, m), 1.95 (1H, m), 3.4 (2H, t, J=11.63 Hz), 3.8 (3H, s), 3.89 (2H, dd, J=4.1 & 11.7 Hz), 4.3 (2H, t, J=7.0 Hz), 7.2 (2H, t, J=7.3 Hz), 7.34 (2H, d, J=8.1 Hz), 7.45 (2H, m), 8.1 (2H, d, J=7.74 Hz).				
8.			(CH ₂) ₄	379	59
	¹ H: 1.0 (2H, m), 1.28 (2H, m), 1.5 (3H, s), 1.54-1.68 (4H, m), 1.9 (1H, m), 3.36 (2H, s), 3.82 (3H, s), 3.89-4.01 (4H, m), 6.9 (2H, m), 7.2 (1H, d, J=7.2 Hz), 7.38 (1H, d, J=7.67 Hz).				
9.			(CH ₂) ₄	365	65
	¹ H: 1.0 (2H, m), 1.3 (2H, m), 1.51 (3H, s), 1.58 (2H, m), 2.0 (1H, m), 3.0 (2H, m), 3.25 (2H, t, J=7.5 Hz), 3.4 (2H, t, J=11.6 Hz), 3.6 (2H, t, J=5.0 Hz), 3.8 (3H, s), 3.94 (2H, dd, J=4.7 & 11.8 Hz), 6.6 (2H, m), 7.0 (2H, m).				
10.			(CH ₂) ₄	413	41
	¹ H: 1.0 (2H, m), 1.35 (2H, m), 1.49 (3H, s), 1.75 (2H, m), 1.98 (1H, m), 3.33 (2H, t, J=11.6 Hz), 3.81 (3H, s), 3.9 (4H, m), 6.8 (2H, d, J=8.3 Hz), 6.9 (2H, t, J=7.5 Hz), 7.1 (4H, m).				

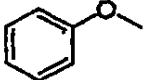
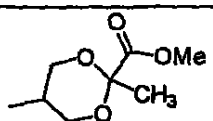
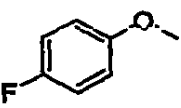
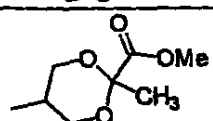
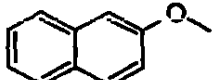
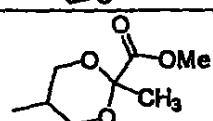
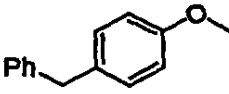
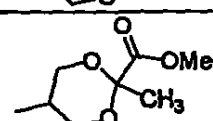
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11.			(CH ₂) ₄	331	43
	¹ H: 1.0 (2H, m), 1.2 (2H, m), 1.5 (3H, s), 1.7 (2H, m), 2.0 (1H, m), 3.3 (2H, t, J=11.6 Hz), 3.8 (3H, s), 3.9 (2H, dd, J=12.0 & 4.6 Hz), 4.1 (2H, t, J=6.9 Hz), 6.5 (1H, d, J=3.0 Hz), 7.0 (1H, d, J=3.1 Hz), 7.1 (1H, d, J=7.5 Hz), 7.2 (1H, t, J=7.2 Hz), 7.3 (1H, d, J=8.2 Hz), 7.6 (1H, d, J=7.8 Hz).				
12.			(CH ₂) ₄	383	41
	¹ H: 0.93-1.0 (2H, m), 1.24 (2H, m), 1.49 (3H, s), 1.52-1.62 (2H, m), 1.95-1.99 (2H, m), 2.06 (1H, m), 3.34 (2H, t, J=11.55 Hz), 3.81 (3H, s), 3.90 (2H, q, J=11.9 & 4.5 Hz), 3.9 (1H, t, J=7.68 Hz), 7.05-7.39 (7H, m), 7.51-7.56 (1H, m), 8.55 (1H, t, J=5.04 Hz).				
13.			(CH ₂) ₄	398	98
	¹ H: 1.04-1.120 (2H, m), 1.37-1.47 (2H, m), 1.51 (3H, s), 1.68-1.80 (2H, m), 2.04 (1H, m), 3.40 (2H, t, J=11.65 Hz), 3.83 (3H, s), 3.89-3.99 (6H, m), 6.74-6.82 (2H, m), 7.04-7.10 (2H, m), 7.15-7.20 (3H, m), 7.27-7.30 (2H, m).				
14.			(CH ₂) ₄	363	80
	¹ H: 1.05-1.11 (2H, m), 1.25-1.38 (2H, m), 1.50 (3H, s), 1.58-1.71 (2H, m), 2.02 (1H, m), 3.39 (2H, t, J=11.67 Hz), 3.82 (3H, s), 3.88-3.97 (4H, m), 4.58 (2H, s), 6.92-7.04 (4H, m).				
15.			(CH ₂) ₄	407	64
	¹ H: 1.08 (2H, m), 1.34 (2H, m), 1.50 (3H, s), 1.63 (2H, m), 1.99 (1H, m), 2.19 (2H, m), 2.28 (1H, t, J=6.06 Hz exchangeable), 3.40 (2H, m), 3.82 (3H, s), 3.85-4.28 (6H, m), 4.67 (1H, t, J=6.52 Hz), 6.92-7.07 (4H, m).				
16.			(CH ₂) ₄	400	98
17.			(CH ₂) ₃	322	40
	¹ H: 1.03 (2H, q, J=7.65 Hz), 1.5 (3H, s), 2.0 - 2.06 (1H, m), 2.50 (2H, t, J=7.5 Hz), 3.41 (2H, t, J=11.75 Hz), 3.49 (2H, t, J=5.13 Hz), 3.82 (3H, s), 3.82 - 3.96 (2H, dd, J= 4.56 & 11.98 Hz), 5.92 (2H, s), 6.57 (1H, t, J=7.83 Hz), 6.62 (1H, s), 6.72 (1H, d, J=7.83 Hz).				

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18.			(CH ₂) ₄	398	46
	¹ H: 1.06 (2H, m), 1.22-1.32 (2H, m), 1.5 (3H, s), 1.59 - 1.61 (2H, m), 1.96 - 2.04 (1H, m), 2.52 (2H, t, J=7.6 Hz), 3.37 (2H, t, J=11.64 Hz), 3.82 (3H, s), 3.9 - 3.96 (2H, dd, J= 4.53 & 11.93 Hz), 5.03 (2H, s), 6.88 (2H, d, J=8.13 Hz), 7.05 (2H, d, J=8.47 Hz), 7.29-7.44 (5H, m).				
19.			(CH ₂) ₄	386	80
20.			(CH ₂) ₃	387	57
	¹ H: 1.19-1.28 (2H, m), 1.34 (3H, t, J=7.11 Hz), 1.56 (3H, s), 1.71-1.76 (2H, m), 2.04-2.11 (1H, m), 3.41-3.49 (2H, m), 3.88 (2H, t, J=6.13 Hz), 3.96-3.99 (2H, m), 4.29 (2H, q, J=7.11 Hz), 6.72-6.78 (2H, m), 7.35 (2H, d, J=8.88 Hz).				
21.			(CH ₂) ₃	308	15
22.			(CH ₂) ₃	389	65
	¹ H: 1.14-1.19 (2H, m), 1.5 (3H, s), 1.60-1.70 (2H, m), 2.01 (1H, m), 2.83-2.94 (2H, m), 3.39 (2H, m), 3.83 (3H, s), 3.92 (2H, dd, J=11.88 & 4.92 Hz), 7.15 (2H, d, J=8.37 Hz), 7.39 (2H, d, J=8.4 Hz).				
23.			(CH ₂) ₃	386	40
24.			(CH ₂) ₃	336	21
25.			(CH ₂) ₃	310	19
26.			(CH ₂) ₃	324	47
27.			(CH ₂) ₃	338	47
28.			(CH ₂) ₃	400	61

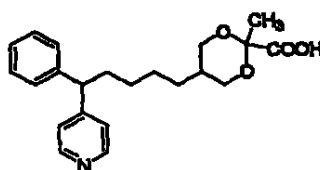
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29.			$(CH_2)_3$	294	11
30.			$(CH_2)_3$	312	33
31.			$(CH_2)_3$	344	20
32.			$(CH_2)_3$	384	24

Preparation 5

2-Methyl-5-(5-phenyl-5-pyridin-4-yl-pentyl)-[1,3]dioxane-2-carboxylic acid
(compound No.37)

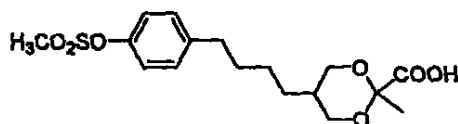
5



To a methanolic solution (10 mL) of methyl-[2-methyl-5-(5-phenyl-5-pyridin-4-yl-pentyl)-[1,3]dioxane-2-carboxylate (compound No.12) (233 mg), prepared as in preparation 1 above was added a solution of sodium hydroxide (50 mg) in water (5 mL) and the reaction mixture was stirred at ambient temperature for 15 hours. The solvents were evaporated under reduced pressure and water (25 mL) was added to the residue. The mixture was acidified with 1 N hydrochloric acid and extracted with ethyl acetate (3 X 20 mL). The combined organic extract was washed with water (25 mL), brine (25 mL), dried over sodium sulfate and evaporated under reduced pressure. The thick gummy product obtained was triturated with petroleum ether to yield 150 mg of product.

Preparation 6

5-[4-(4-Methanesulfonyloxy-phenyl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylic acid
(compound No.50)

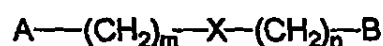


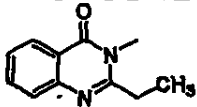
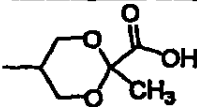
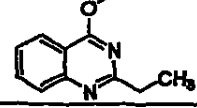
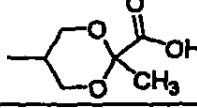
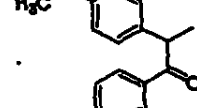
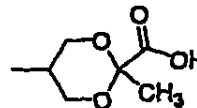
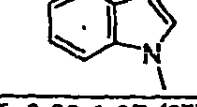
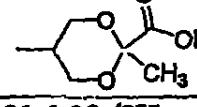
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To a solution of Methyl-5-[4-(4-methanesulfonyloxy-phenyl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylate (compound No.19) (166 mg) in tetrahydrofuran (2 mL)

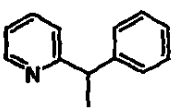
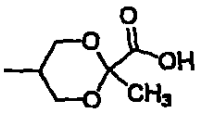
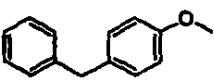
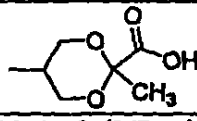
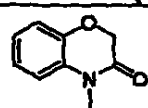
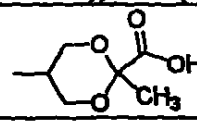
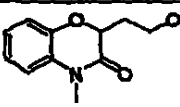
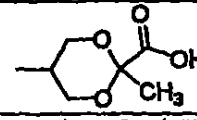
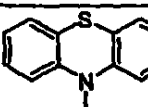
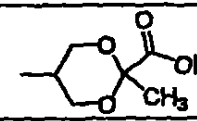
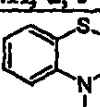
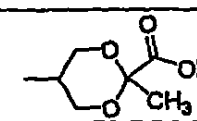
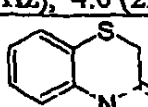
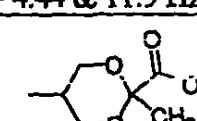
was added another solution of lithium hydroxide (21 mg) in water (3 mL) and the reaction mixture was stirred at ambient temperature for 18 hours. Reaction mixture was diluted with water (20 mL), acidified to pH 2-3 with 1N hydrochloric acid and extracted with ethyl acetate (3 X 10 mL). The combined organic extract was washed with water (20 mL), brine solution (20 mL), dried over sodium sulfate and evaporated under reduced pressure to obtain 127 mg of product.

Table 2:

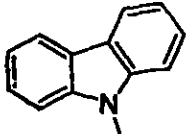
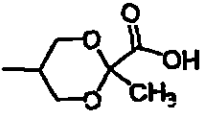
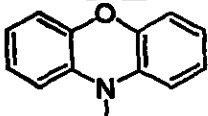
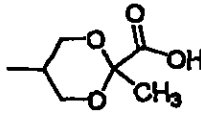
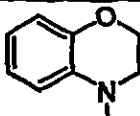
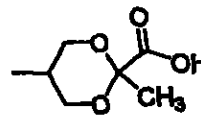
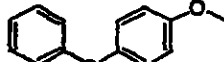
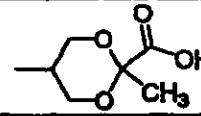
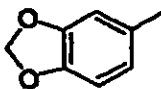
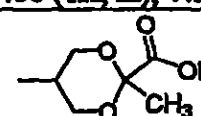
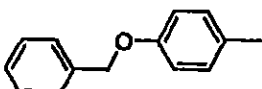
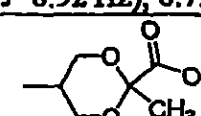
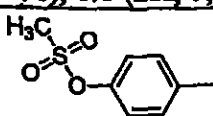
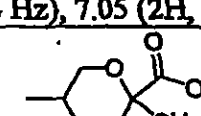


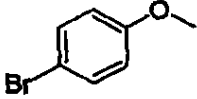
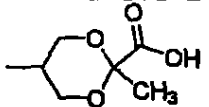
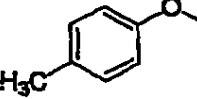
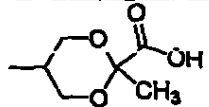
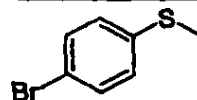
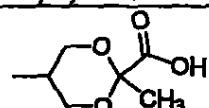
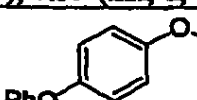
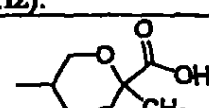
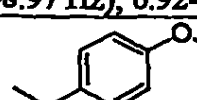
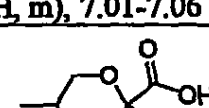
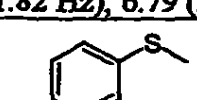
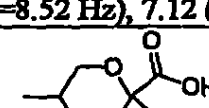
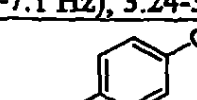
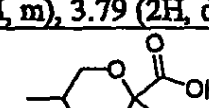
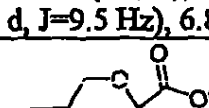
S.No.	A	B	$-(CH_2)_m-X-(CH_2)_n-$	Mol. Wt.	% Yield
33.			$(CH_2)_4$	374	58
	¹ H: 1.1 (2H, m), 1.2 (2H, m), 1.4 (3H, t, J=7.4 Hz), 1.52 (3H, s), 1.7 (2H, m), 2.0 (1H, m), 2.8 (2H, q, J=7.4 Hz), 3.5 (2H, t, J=11.5 Hz), 3.9 (2H, dd, J=11.8 & 4.5 Hz), 4.0 (2H, t, J=7.9 Hz), 7.4 (1H, t, J=7.3 Hz), 7.6 (1H, d, J=8.1 Hz), 7.7 (1H, t, J=7.2 Hz), 8.2 (1H, d, J=7.5 Hz).				
34.			$(CH_2)_4$	374	66
	¹ H: 1.1 (2H, m), 1.2 (2H, m), 1.4 (3H, t, J=7.5 Hz), 1.5 (3H, s), 1.8 (2H, m), 2.0 (1H, s), 3.0 (2H, q, J=7.5 Hz), 3.5 (2H, t, J=11.5 Hz), 3.9 (2H, dd, J=11.7 & 4.3 Hz), 4.6 (2H, t, J=6.3 Hz), 7.5 (1H, t, J=7.3 Hz), 7.8 (1H, t, J=7.1 Hz), 7.9 (1H, d, J=8.4 Hz), 8.1 (1H, d, J=8.2 Hz).				
35.			$(CH_2)_4$	476.5	97
	¹ H: 1.0 (2H, m), 1.2 (2H, m), 1.55 (3H, s), 1.7 (2H, m), 1.9-2.1 (3H, m), 2.4 (3H, s), 3.4 (2H, t, J=11.8 Hz), 3.9 (2H, dd, J=11.7 & 4.4 Hz), 4.3 (1H, t, J=7.15 Hz), 7.16 (4H, m), 7.3 (2H, d, J=8.46 Hz), 7.8 (2H, d, J=8.48 Hz).				
36.			$(CH_2)_4$	317	59
	¹ H: 0.99-1.07 (2H, m), 1.21-1.32 (2H, m), 1.55 (3H, s), 1.76-1.85 (2H, m), 1.98 (1H, m), 3.41 (2H, t, J=11.59 Hz), 3.92 (2H, dd, J= 12.0 & 4.5 Hz), 4.10 (2H, t, J=6.90 Hz), 6.48 (1H, d, J=3.03 Hz), 7.05 (1H, t, J=3.0 Hz), 7.10 (1H, d, J=7.12 Hz), 7.19 (1H, t, J=7.05 Hz), 7.30 (1H, d, J=8.19 Hz), 7.62 (1H, d, J=7.83 Hz).				

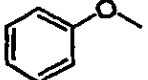
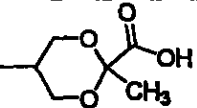
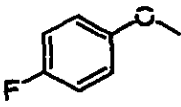
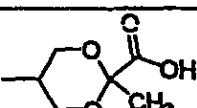
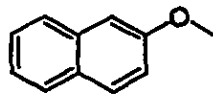
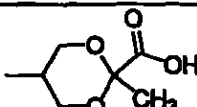
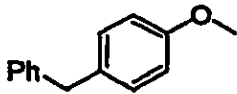
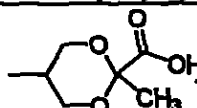
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37.			(CH ₂) ₄	369	55
	¹ H: 0.96 (2H, d, J=6.72 Hz), 1.27 (2H, d, J=6.66 Hz), 1.59 (3H, s), 2.10 (5H, m), 3.43-3.52 (2H, m), 3.93 (2H, q, J=11.55 & 4.26 Hz), 4.28 (1H, t, J=7.65 Hz), 7.14-7.23 (3H, m), 7.31 (4H, m), 7.65 (1H, t, J=7.74 Hz), 8.63 (1H, d, J=4.74 Hz).				
38.			(CH ₂) ₄	384	40
	¹ H: 1.10-1.15 (2H, m), 1.38-1.48 (2H, m), 1.57 (3H, s), 1.63-1.78 (2H, m), 2.05 (1H, m), 3.46 (2H, t, J=11.15 Hz), 3.88-3.94 (4H, m), 3.97-4.02 (2H, dd, J=11.97 & 4.5 Hz), 6.77-6.80 (2H, d, J=8.49 Hz), 7.08 (2H, d, J=8.37 Hz), 7.15-7.29 (5H, m).				
39.			(CH ₂) ₄	349	48
	¹ H: 1.07-1.15 (2H, m), 1.29-1.34 (2H, m), 1.57 (3H, s), 1.59-1.69 (2H, m), 2.03 (1H, m), 3.47 (2H, t, J=11.49 Hz), 3.89-4.02 (4H, m), 4.59 (2H, s), 6.93-7.05 (4H, m).				
40.			(CH ₂) ₄	393	24
	¹ H: 1.12 (2H, m), 1.28 (2H, m), 1.55 (3H, s), 1.64 (2H, dd, J=7.27 & 14.57 Hz), 2.03 (1H, m), 2.20 (2H, m), 3.48 (2H, m), 3.91 (6H, m), 4.67 (1H, t, J=6.44 Hz), 6.99 (4H, m).				
41.			(CH ₂) ₄	399	66
	¹ H: 1.0 (2H, m), 1.36 (2H, m), 1.5 (3H, s), 1.76 (2H, m), 2.0 (1H, m), 3.4 (2H, t, J=11.5 Hz), 3.9 (2H, m), 3.96 (2H, dd, J=4.5 & 11.9 Hz), 6.84 (2H, m), 6.91 (2H, m), 7.15 (4H, d, J=7.0 Hz).				
42.			(CH ₂) ₄	351	84
	¹ H: 1.1 (2H, m), 1.3 (2H, m), 1.57 (3H, s), 1.6 (2H, m), 2.05 (1H, m), 3.0 (2H, dd, J=3.0 & 5.2 Hz), 3.25 (2H, t, J=7.5 Hz), 3.47 (2H, t, J=11.5 Hz), 3.6 (2H, dd, J=5.1 & 7.0 Hz), 4.0 (2H, dd, J=4.44 & 11.9 Hz), 6.6 (2H, m), 7.0 (2H, m).				
43.			(CH ₂) ₄	365	93
	¹ H: 1.1 (2H, m), 1.3 (2H, m), 1.56 (3H, s), 1.6 (2H, m), 2.0 (1H, m), 2.4 (1H, bs), 3.37 (2H, s), 3.48 (2H, t, J=11.5 Hz), 4.0 (4H, m), 7.0 (2H, m), 7.2 (1H, m), 7.38 (1H, d, J=7.5 Hz).				

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44.			(CH ₂) ₄	367	74
	¹ H: 1.04 (3H, m), 1.3 (2H, m), 1.53 (3H, s), 1.84 (2H, m), 1.95 (1H, m), 3.4 (2H, t, J=11.5 Hz), 3.9 (2H, dd, J=4.4 & 11.8 Hz), 4.3 (2H, t, J=7.0 Hz), 7.2 (2H, t, J=7.3 Hz), 7.34 (2H, d, J=8.1 Hz), 7.45 (2H, m), 8.1 (2H, d, J=7.71 Hz).				
45.			(CH ₂) ₄	383	70
	¹ H: 1.11 (2H, m), 1.4 (2H, m), 1.57 (3H, s), 1.6 (2H, m), 2.0 (1H, m), 3.5 (4H, t, J=11.5 Hz), 4.0 (2H, dd, J=4.4 & 11.8 Hz), 6.4 (2H, d, J=7.84 Hz), 6.6 (4H, m), 6.77 (2H, m).				
46.			(CH ₂) ₄	335	56
	¹ H: 1.08 (2H, m), 1.3 (2H, m), 1.52-1.62 (5H, m), 2.04 (1H, m), 3.2 (2H, t, J=7.4 Hz), 3.3 (2H, t, J=4.3 Hz), 4.7 (2H, t, J=11.6 Hz), 4.0 (2H, dd, J=4.4 & 11.8 Hz), 4.22 (2H, t, J=4.3 Hz), 6.6 (2H, d, J=7.5 Hz), 6.8 (2H, m).				
47.			(CH ₂) ₄	386	90
	¹ H: 1.1 (2H, m), 1.4 (2H, m), 1.5 (3H, s), 1.7 (2H, m), 2.0 (1H, m), 3.44-3.52 (2H, m), 3.9 (2H, t, J=6.09 Hz), 4.04 (2H, dd, J=4.41 & 11.85 Hz), 6.83 (2H, d, J=8.97 Hz), 6.92-6.97 (4H, m), 7.01-7.06 (1H, m), 7.30 (2H, d, J=7.95 Hz).				
48.			(CH ₂) ₃	308	85
	¹ H: 1.07 (2H, q, J=7.5 Hz), 1.48-1.54 (2H, m), 1.57 (3H, s), 2.01-2.08 (1H, m), 2.50 (2H, t, J=7.47 Hz), 3.45 (2H, t, J=11.58 Hz), 3.95-4.0 (2H, dd, J=4.46 & 11.95 Hz), 5.92 (2H, s), 6.59 (2H, t, J=8.92 Hz), 6.72 (1H, d, J=7.86 Hz).				
49.			(CH ₂) ₄	384	84
	¹ H: 1.04-1.09 (2H, m), 1.23-1.33 (4H, m), 1.53 (3H, s), 1.97-2.05 (1H, m), 2.52 (2H, t, J=7.57 Hz), 3.43 (2H, t, J=11.52 Hz), 3.94-3.99 (2H, dd, J=4.49 & 11.8 Hz), 5.03 (2H, s), 6.8 (2H, d, J=8.4 Hz), 7.05 (2H, d, J=8.43 Hz), 7.29-7.44 (5H, m).				
50.			(CH ₂) ₄	372	80
	¹ H: 1.03-1.10 (2H, q, J=7.51 Hz), 1.28-1.34 (2H, m), 1.53 (3H, s), 1.6 (2H, m), 1.98-2.04 (1H, m), 2.59 (2H, t, J=7.56 Hz), 3.13 (3H, s), 3.44 (2H, t, J=11.65 Hz), 3.93-3.99 (2H, dd, J=4.68 & 11.94 Hz), 7.18 (4H, s).				

51.			(CH ₂) ₃	359	45
	¹ H: 1.20-1.28 (2H, m), 1.58 (3H, s), 1.70-1.79 (2H, m), 2.05-2.13 (1H, m), 3.8 (2H, t, J=6.075 Hz), 4.0-4.05 (2H, m), 6.73 (2H, d, J=8.82 Hz), 7.35 (2H, d, J=8.85 Hz).				
52.			(CH ₂) ₃	294	74
	¹ H: 1.20-1.28 (2H, m), 1.58 (3H, s), 1.71-1.76 (2H, m), 2.1 (1H, m), 2.27 (3H, s), 3.46-3.54 (2H, m), 3.89 (2H, t, J=6.13 Hz), 4.03 (2H, dd, J=11.88 & 4.47 Hz), 6.76 (2H, d, J=8.43 Hz), 7.06 (2H, d, J=8.34 Hz).				
53.			(CH ₂) ₃	375	10
	¹ H: 1.15-1.18 (2H, m), 1.5 (3H, s), 1.59-1.6 (2H, m), 1.99-2.06 (1H, m), 2.85 (2H, t, J=7.06 Hz), 3.42-3.49 (2H, m), 3.95 (2H, dd, J=11.88 & 4.34 Hz), 7.16 (2H, d, J=8.4 Hz), 7.39 (2H, d, J=8.43 Hz).				
54.			(CH ₂) ₃	372	37
	¹ H: 1.22-1.29 (2H, m), 1.72 (3H, s), 1.73-1.78 (2H, m), 2.04-2.14 (1H, m), 3.47-3.55 (2H, m), 3.9 (2H, t, J=6.09 Hz), 4.04 (2H, dd, J=4.41 & 11.85 Hz), 6.83 (2H, d, J=8.97 Hz), 6.92-6.97 (4H, m), 7.01-7.06 (1H, m), 7.30 (2H, d, J=7.95 Hz).				
55.			(CH ₂) ₃	322	67
	¹ H: 1.22 (6H, s), 1.25-1.28 (2H, m), 1.58 (3H, s), 1.69-1.78 (2H, m), 2.1 (1H, m), 2.80-2.89 (1H, m), 3.46-3.54 (2H, m), 3.90 (2H, t, J=6.1 Hz), 4.02 (2H, dd, J=4.62 & 11.82 Hz), 6.79 (2H, d, J=8.52 Hz), 7.12 (2H, d, J=8.52 Hz).				
56.			(CH ₂) ₃	296	77
	¹ H: 1.12-1.04 (2H, m), 1.31 (3H, s), 1.44-1.54 (2H, m), 1.83-1.84 (1H, m), 2.90 (2H, t, J=7.1 Hz), 3.24-3.32 (2H, m), 3.79 (2H, dd, J=4.2 & 11.46 Hz), 7.13-7.29 (5H, m).				
57.			(CH ₂) ₃	310	82
	¹ H: 1.20-1.28 (2H, q, J=7.6 Hz), 1.58 (3H, s), 1.63-1.77 (2H, m), 2.07-2.13 (1H, m), 3.5 (2H, t, J=11.5 Hz), 3.76 (3H, s), 3.87 (2H, t, J=6.1 Hz), 4.0-4.06 (2H, dd, J=4.4 & 4.5 Hz), 6.7 (2H, d, J=9.5 Hz), 6.83 (2H, d, J=4.57 Hz).				
58.			(CH ₂) ₃	386	71
	¹ H: 1.20-1.28 (2H, q, J=7.5 Hz), 1.58 (3H, s), 1.70-1.82 (2H, m), 2.05-2.11 (1H, m), 3.5 (1H, t, J=11.5 Hz), 3.82-4.0 (5H, m), 5.0 (2H, s), 6.77-6.91 (4H, m), 7.25 (1H, s), 7.28-7.42 (4H, m).				

59.			$(CH_2)_3$	280	55
	^1H : 1.07-1.14 (2H, q, $J=7.5$ Hz), 1.32 (3H, s), 1.60-1.69 (2H, m), 1.84-1.92 (1H, m), 3.32-3.36 (2H, m), 3.84-3.95 (4H, m), 6.89 (3H, t, $J=6.51$ Hz), 7.25 (2H, t, $J=7.89$ Hz).				
60.			$(CH_2)_3$	298	82
	^1H : 1.21-1.29 (2H, m), 1.59 (3H, s), 1.70-1.79 (2H, m), 2.0-2.14 (1H, m), 3.47-3.5 (2H, m), 3.86-3.92 (2H, m), 4.10-4.06 (2H, dd, $J=4.5$ & 11.7 Hz), 6.77-6.82 (2H, m), 6.97 (2H, d, $J=8.7$ Hz).				
61.			$(CH_2)_3$	330	83
	^1H : 1.26-1.34 (2H, q, $J=7.76$ Hz), 1.59 (3H, s), 1.76-1.90 (2H, m), 2.10-2.17 (1H, m), 3.49-3.57 (2H, m), 4.0-4.12 (4H, m), 7.1 (2H, d, $J=9$ Hz), 7.32 (1H, t, $J=7.23$ Hz), 7.43 (1H, t, $J=7.25$ Hz), 7.69-7.7 (3H, m).				
62.			$(CH_2)_3$	370	80
	^1H : 1.20-1.27 (2H, q, $J=7.6$ Hz), 1.58 (3H, s), 1.58-1.71 (2H, m), 2.0-2.11 (1H, m), 3.46-3.54 (2H, m), 3.87-3.96 (4H, m), 3.99-4.0 (2H, dd, $J=4.65$ & 11.8 Hz), 6.8 (2H, d, $J=7.72$ Hz), 7.0 (2H, d, $J=8.43$ Hz), 7.17 (3H, d, $J=7.73$ Hz), 7.24-7.29 (2H, m).				

Preparation of salts

Sodium and potassium salts of the compounds in table 2 were prepared by following the general procedure described below.

To a solution of carboxylic acid derivatives of the novel compounds (mentioned in table 2) (1 mmol) in alcoholic solvent like methanol, ethanol and the like was added another solution of sodium or potassium alkoxide (0.95 mmol) in alcoholic solvent and the reaction mixture was stirred for 3 hours at 25-30 °C. The solvent was evaporated and the residue was triturated with dry diethyl ether or diisopropyl ether to obtain the salt of the corresponding carboxylic acid.

The compounds of the present invention lowered triglyceride, total cholesterol, LDL, VLDL and increased HDL and lowered serum glucose levels. This was demonstrated by *in vivo* animal experiments.

A) Demonstration of *in vivo* efficacy of compounds:

i) Serum triglyceride and total cholesterol lowering activity in Swiss albino mice:

Male Swiss albino mice (SAM) were bred in Zydus animal house. All these animals were maintained under 12 hour light and dark cycle at 25 ± 1 °C. Animals were given standard laboratory chow (NIN, Hyderabad, India) and water ad libitum. SAM of 20-30 g body weight range was used. The protocol approved by Institutional Animal Ethics Committee is being used.

The test compounds were administered orally to Swiss albino mice at 0.001 to 50 mg / kg/ day dose for 6 days. The compound was administered after suspending it in 0.25 % CMC or dissolving it in water, when compound is water-soluble. Control mice were treated with vehicle (0.25 % of Carboxymethylcellulose; dose 10 ml/kg).

The blood samples were collected on 0th day and in fed state 1 hour after drug administration on 6th day of the treatment. The blood was collected in non heparinised capillary and the serum was analyzed for triglyceride and total cholesterol (Wieland, O, Methods of Enzymatic analysis. Bergermeyer, H, O., Ed., 1963. 211-214; Trinder, P. Ann. Clin. Biochem. 1969. 6: 24-27). Measurement of serum triglyceride and total cholesterol was done using commercial kits (Zydus-Cadila, Pathline, Ahmedabad, India).

Formula for calculation:

Percentage reduction in triglycerides/total cholesterol were calculated according to the formula:

Percentage reduction (%) =

$$1 - \left[\frac{TT/OT}{TC/OC} \right] \times 100$$

OC = Zero day control group value OT = Zero day treated group value

TC = Test day control group TT = Test day treated group

Table 1:

Triglyceride lowering activity in Swiss albino mice:

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Example No.	Dose (mg/kg/day)	% Triglyceride lowering
50	10	32
38	10	32
49	10	26

ii) Serum triglyceride and total cholesterol lowering activity in Hamster of Syrian golden stain:

Male and Female Hamster of Syrian golden stain were bred in Zydus animal house. All these animals were maintained under 12-hour light and dark cycle at 22 ± 3 degree C. The protocol approved by Institutional Animal Ethics Committee is being used. Two groups of animals were put on HF-HC (High fat and high cholesterol) diet for 14 days. On day 14 all the HF-HC diet whereas one group of animals of were put on normal diet for two weeks.

One group of animals on HF-HC diet were treated (po) with compounds of the present invention, at 0.001 to 50 mg / kg daily for 15 days while the other group received the vehicle. After 15 days blood samples were be collected in non heparinized capillary from animals for determination of total cholesterol (TC), triglyceride (TG) (Wieland, O. Methods of Enzymatic analysis. Bergermeyer, H., O., Ed., 1963. 211-214; Trinder, P. Ann. Clin. Biochem. 1969. 6: 24-27). Measurement of serum triglyceride and total cholesterol was done using commercial kits (Pointe Scientific.Inc.USA.)

Formula for calculation:
Percentage reduction in triglycerides/total cholesterol were calculated according to the formula:

Percentage reduction (%) = $(TT-TC)/TC \times 100$
TC = Test day control group TT = Test day treated group.

Table 2.

Example No.	Dose (mg/kg/day)	% Triglyceride lowering
50	3	45

No adverse effects were observed for any of the mentioned compounds of invention. The compounds of the present invention showed good serum glucose, lipid and cholesterol lowering activity in the experimental animals used. These compounds

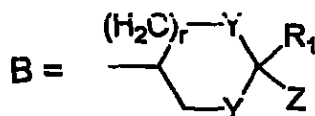
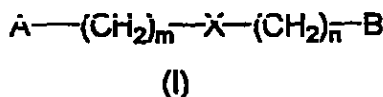
are useful for the testing / prophylaxis of diseases caused by hyperlipidemia, hypercholesterolemia, hyperinsulinemia, hyperglycemia such as NIDDM. cardiovascular diseases, stroke, hypertension, obesity since such diseases are interlinked to each other.

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We claim:

A compound of formula (I):



- 5 their tautomeric forms, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, pharmaceutical compositions containing them, wherein 'A' represents optionally substituted, single or fused aryl, cycloalkyl group or an optionally substituted heteroaryl or an optionally substituted heterocyclyl group; 'm' = 0-2; 'n' = 3-6; 'X' represents O, S, -N-(Ra)- or -CH₂-; Ra represents H, linear or branched, group
- 10 selected from alkyl, acyl or aryl, aralkyl group, which may optionally be substituted; 'Y' at each occurrence independently represent O or S; R₁ represents H, linear or branched substituted or unsubstituted alkyl; r = 0-2; Z represents -(CH₂)_sCOOH, alkoxycarbonyl, hydroxymethyl, -CN, substituted or unsubstituted tetrazoles, alkylcarbonyl groups, s = 0-4; with the proviso that when 'X' = CH₂ and
- 15 i) 'A' represents substituted heterocyclic group, the substitutions on 'A' does not represent aryl, aromatic, heterocyclic or cycloalkyl group; and
- ii) 'A' represents substituted aryl group, the substituent on 'A' represents alkylsulfonyloxy, aryloxy, aralkoxy, cycloalkyl, heteroaryl or heterocyclic group.
- 20 2. A compound as claimed in claim 1 wherein, when 'A' is substituted, suitable substitutions on 'A' may be selected from hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from amidino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, acyl, acyloxy, acylamino,
- 25 monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkylsulfonylamino, alkylsulfonyloxy, alkoxycarbonylamino,
- 30 aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino,

alkylaminocarbonylamino, alkoxyamino, hydroxyl amino, sulfenyl derivatives, sulfonyl derivatives.

3. A compound as claimed in claim 1 wherein suitable substitutions on 'B' may be selected from hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from alkyl, haloalkyl, aryl groups

- 5 (4) A compound as claimed in claim 1 wherein, the substitutions on any of the substituents on 'A' & 'B' may be selected from hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from amidino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, 10 cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, 15 alkylsulfonylamino, alkylsulfonyloxy, alkoxycarbonylamino, aryloxcarbonylamino, aralkyloxcarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkoxyamino, hydroxyl amino, sulfenyl derivatives, sulfonyl derivatives.

- (5) The compounds of claim 1-3 selected from
- 20 Methyl-5-[4-(2-ethyl-4-oxo-4H-quinazolin-3-yl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylate;
Methyl-5-[4-(2-ethyl-quinazolin-4-yloxy)-butyl]-2-methyl-[1,3]dioxane-2-carboxylate;
Methyl-5-[6-(4-chloro-phenyl)-5-(4-methylsulfonyl-phenyl)-6-oxo-hexyl]-2-methyl-[1,3]dioxane-2-carboxylate;
- 25 Methyl-5-[4-(2,3-dihydro-benzo[1,4]oxazin-4-yl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylate;
Methyl-2-methyl-5-(4-phenoxazin-10-yl-butyl)-[1,3]dioxane-2-carboxylate;
Methyl-5-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylate;
- 30 Methyl-5-(4-carbazol-9-yl-butyl)-2-methyl-[1,3]dioxane-2-carboxylate;
Methyl-2-methyl-5-[4-(3-oxo-2,3-dihydro-benzo[1,4]thiazin-4-yl)-butyl]-[1,3]dioxane-2-carboxylate;
Methyl-5-[4-(2,3-dihydro-benzo[1,4]thiazin-4-yl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylate,

- Methyl-2-methyl-5-(4-phenothiazin-10-yl-butyl)-[1,3]dioxane-2-carboxylate;
Methyl-5-(4-indol-1-yl-butyl)-2-methyl-[1,3]dioxane-2-carboxylate;
Methyl-2-methyl-5-(5-phenyl-5-pyridin-4-yl-pentyl)-[1,3]dioxane-2-carboxylate;
Methyl-5-[4-(4-benzyl-phenoxy)-butyl]-2-methyl-[1,3]dioxane-2-carboxylate;
5 Methyl-2-methyl-5-[4-(3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-butyl]-[1,3]dioxane-2-carboxylate;
Methyl-5-{4-[2-(2-hydroxy-ethyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl]-butyl}-2-methyl-[1,3]dioxane-2-carboxylate;
Methyl-2-methyl-5-[4-(4-phenoxy-phenoxy)-butyl]-[1,3]dioxane-2-carboxylate;
10 Methyl-5-(3-benzo[1,3]dioxol-5-yl-propyl)-2-methyl-[1,3]dioxane-2-carboxylate;
Methyl-5-[4-(4-methanesulfonyloxy-phenyl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylate;
Methyl-5-[4-(4-benzyloxy-phenyl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylate;
Methyl-2-methyl-5-(3-phenylsulfanyl-propyl)-[1,3]dioxane-2-carboxylate;
15 Ethyl-5-[3-(4-bromo-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylate;
Methyl-2-methyl-5-[3-(4-phenoxy-phenoxy)-propyl]-[1,3]dioxane-2-carboxylate;
Methyl-5-[3-(4-isopropyl-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylate;
Methyl-2-methyl-5-(3-p-tolyloxy-propyl)-[1,3]dioxane-2-carboxylate;
Methyl-5-[3-(4-bromo-phenylsulfanyl)-propyl]-2-methyl-[1,3]dioxane-2-carboxylate;
20 Methyl-2-methyl-5-(3-phenoxy-propyl)-[1,3]dioxane-2-carboxylate;
Methyl-5-[3-(4-fluoro-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylate;
Methyl-2-methyl-5-[3-(naphthalen-2-yloxy)-propyl]-[1,3]dioxane-2-carboxylate;
Methyl-5-[3-(4-benzyloxy-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylate;
Methyl-5-[3-(4-methoxy-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylate;
25 Methyl-5-[3-(4-benzyl-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylate;
5-[4-(2-Ethyl-4-oxo-4H-quinazolin-3-yl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
5-[4-(2-Ethyl-quinazolin-4-yloxy)-butyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
30 5-[6-(4-Chloro-phenyl)-5-(4-methylsulfanyl-phenyl)-6-oxo-hexyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
5-[4-(2,3-Dihydro-benzo[1,4]oxazin-4-yl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts,

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- 2-Methyl-5-(4-phenoxazin-10-yl-butyl)-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 5-(4-Carbazol-9-yl-butyl)-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 5 2-Methyl-5-[4-(3-oxo-2,3-dihydro-benzo[1,4]thiazin-4-yl)-butyl]-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts,
- 5-[4-(2,3-Dihydro-benzo[1,4]thiazin-4-yl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 2-Methyl-5-(4-phenothiazin-10-yl-butyl)-[1,3]dioxane-2-carboxylic acid and its
- 10 pharmaceutically acceptable salts;
- 5-(4-Indol-1-yl-butyl)-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 2-Methyl-5-(5-phenyl-5-pyridin-4-yl-pentyl)-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 15 5-[4-(4-Benzyl-phenoxy)-butyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 2-Methyl-5-[4-(3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-butyl]-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 5-{4-[2-(2-Hydroxy-ethyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl]-butyl}-2-methyl-
- 20 [1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 2-Methyl-5-[4-(4-phenoxy-phenoxy)-butyl]-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 5-(3-Benzo[1,3]dioxol-5-yl-propyl)-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 25 5-[4-(4-Methanesulfonyloxy-phenyl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 5-[4-(4-Benzoyloxy-phenyl)-butyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 2-Methyl-5-(3-phenylsulfanyl-propyl)-[1,3]dioxane-2-carboxylic acid and its
- 30 pharmaceutically acceptable salts;
- 5-[3-(4-Bromo-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 2-Methyl-5-[3-(4-phenoxy-phenoxy)-propyl]-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;

- 5-[3-(4-Isopropyl-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 2-Methyl-5-(3-p-tolyloxy-propyl)-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 5 5-[3-(4-Bromo-phenylsulfanyl)-propyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 2-Methyl-5-(3-phenoxy-propyl)-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 10 5-[3-(4-Fluoro-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 2-Methyl-5-[3-(naphthalen-2-yloxy)-propyl]-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 5-[3-(4-Benzylphenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 15 5-[3-(4-Methoxy-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 5-[3-(4-Benzyl-phenoxy)-propyl]-2-methyl-[1,3]dioxane-2-carboxylic acid and its pharmaceutically acceptable salts;
- 20 6. A pharmaceutical composition which comprises compounds of formula (I), as claimed in any preceding claims and a pharmaceutically acceptable carrier, diluent, excipients or solvate.
7. A method of preventing or treating diseases caused by hyperlipidaemia, hypercholesteremia, hyperglycemia, obesity, impaired glucose tolerance, leptin resistance, insulin resistance, diabetic complications, comprising administering an effective, non-toxic amount of compound of formula (I) or suitable pharmaceutical composition as defined in any preceding claims to a patient in need thereof.
- 25 8. The method according to any preceding claims, wherein the disease is type 2 diabetes, impaired glucose tolerance, dyslipidaemia, hypertension, obesity, atherosclerosis, hyperlipidaemia, coronary artery disease, cardiovascular disorders and other diseases wherein insulin resistance is the underlying pathophysiological mechanism.
- 30 9. A medicine for treating/reducing any of the disease conditions described in any preceding claims which comprises administering a compound of formula (I), as

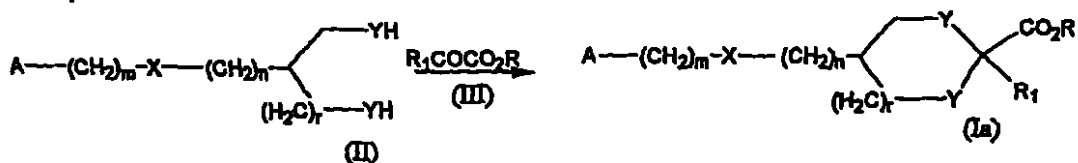
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defined in claims 1-5 and a pharmaceutically acceptable carrier, diluent, excipients or solvate to a patient in need thereof

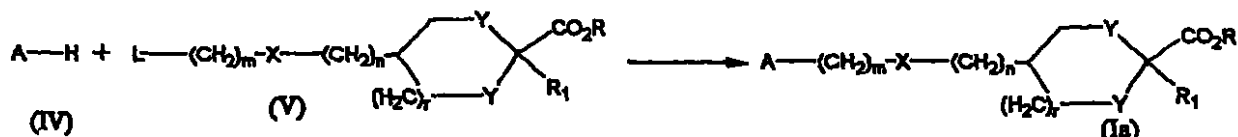
10. Use of compounds of formula (I), their pharmaceutical compositions and medicines containing them as defined in any previous claims as a medicament suitable for the treatment of diseases mentioned in any of the aforesaid claims.

11. A process for preparing compound of formula (I) comprising the steps of

i) reacting a compound of formula (II) with a compound of formula (III), where 'R' represents suitable alkyl group and all other symbols are as defined in claim 1, to obtain compounds of formula (Ia)



ii) alternatively, reacting a compound of formula (IV) with a compound of formula (V), where 'L' represents suitable leaving group and 'R' represents suitable alkyl group and all other symbols are as defined in claim 1, to obtain compound of formula (Ia), where all symbols are as defined in claim 1



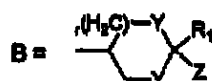
iii) converting the compound of formula (Ia) to compound of formula (I), where all symbols are as defined in claim 1



DERIVADOS DE 1,3-DIOXANO Y ANÁLOGOS DE ESTOS ÚTILES EN EL
TRATAMIENTO DE OBESIDAD Y DIABETES ENTRE OTROS

CAMPO DE LA INVENCION

La presente invención se relaciona con compuestos novedosos de la fórmula general (I), sus forma tautoméricas, sus sales farmacéuticamente aceptables, sus solvatos farmacéuticamente aceptables, las composiciones farmacéuticas que las contienen, el uso de estos compuestos en medicina y los intermedios involucrados en su preparación.



La presente invención también se relaciona con un proceso para la preparación de los compuestos de fórmula (I), sus formas tautoméricas, sus sales farmacéuticamente aceptables, sus solvatos farmacéuticamente aceptables, y las composiciones farmacéuticas que los contienen.

Los compuestos de la fórmula (I) disminuyen los niveles de glucosa en la sangre, disminuyen o modulan los niveles de triglicéridos y/o los niveles de colesterol y/o los niveles de lipoproteínas de baja densidad (LDL) y elevan las lipoproteínas de alta densidad (HDL) y de esta manera son útiles para combatir diferentes condiciones médicas, donde tal disminución (y elevación) es benéfica. Así, estos se

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podrían utilizar en el tratamiento y/o profilaxis de la obesidad, hiperlipidemia, hipercolesterolemia, hipertensión, eventos de enfermedad aterosclerótica, restenosis vascular, diabetes, y muchas otras condiciones relacionadas.

Los compuestos de la fórmula (I) son útiles para prevenir o disminuir el riesgo de desarrollar arterosclerosis, que conduzca a enfermedades y condiciones tales como las enfermedades cardiovasculares, arteroscleróticas, apoplejías, enfermedades cardíacas coronarias, enfermedades cerebrovasculares, enfermedades de los vasos periféricos y desórdenes relacionados.

Los de fórmula (I) son útiles para el tratamiento y/o la profilaxis de los desórdenes metabólicos genéricamente definida como síndrome X. Las características del síndrome X incluyen resistencia a la insulina seguida por hiperinsulinemia, dislipidemia y tolerancia dañada a la glucosa. La intolerancia a la glucosa puede conducir a diabetes melitus no dependiente de insulina (NIDDM, diabetes Tipo 2), que se caracteriza por hiperglicemia, que no es controlada y puede conducir a complicaciones diabéticas o desórdenes metabólicos originados por la resistencia a la insulina. La diabetes ya no es considerada por estar asociada solamente con el metabolismo de la glucosa, sino que esta afecta a los parámetros anatómicos y fisiológicos, cuya intensidad varía dependiendo de las etapas/variación y

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severidad del estado diabético, los compuestos de esta invención también son útiles en la prevención, detención o disminución de la progresión o reducción del riesgo de los desórdenes anteriormente mencionados junto con las enfermedades secundarias resultantes tales como las enfermedades cardiovasculares, como la arteriosclerosis, la aterosclerosis; retinopatía diabética, neuropatía diabética y enfermedad renal que incluye nefropatía diabética, glomerulonefritis, esclerosis glomerular, síndrome nefrótico, nefrosclerosis hipertensiva y enfermedades renales en etapa terminal, como la microalbuminuria y la albuminuria, que pueden dar como resultado la hiperglicemia o hiperinsulinemia.

ANTECEDENTES DE LA INVENCION

La presente invención describe compuestos adecuados para el tratamiento de la hiperlipidemia, la diabetes, la obesidad y enfermedades similares al modular el Receptor Activado Proliferador de Peroxisoma (PPAR). Las condiciones de enfermedad, la patofisiología de las condiciones de la enfermedad, sus efectos y las terapias conocidas y propuestas se han descrito en detalle en la WO 9119702, WO 9401420, WO 9413650, WO 9503038, WO 9517394, WO 9604260, WO 9604261, WO 9633998, WO 9725042, WO 9736579, WO 9828534, WO 9908501, WO 9916758, WO 9919313, WO 9920614, WO 0023417, WO 0023445, WO 0023451, WO 0309841, WO 0066572, WO 0116111, WO 0116120, WO



0153257 etc. que se incorporan en su totalidad como referencia.

La hiperlipidemia se ha reconocido como el factor de riesgo principal en la causa de enfermedades cardiovasculares debido a la aterosclerosis [*MetS Insights*, Sep; 4,13-17 (2004)]. La aterosclerosis y otras enfermedades vasculares periféricas afecta la calidad e vida de una gran población en el mundo. La terapia apunta a disminuir el colesterol LDL elevado en el plasma, las lipoproteínas de baja densidad y las triglicéridos del plasma con el fin de evitar y reducir el riesgo de ocurrencia de enfermedades cardiovasculares. La etiología detallada de la aterosclerosis y las enfermedades arteriales coronarias se discute por Ross y Glomset [*New Engl. J. Med.* , 295,369-377 (1976)].

El Receptor Activado Proliferador de Peroxisoma (PPAR) es un miembro de la familia receptora de la hormona esteroide/retinoide/tiroide. El PPAR α , PPAR γ y PPAR δ se han identificado como subtipos de los PPAR. El papel del PPAR en diferentes condiciones de enfermedad es la activación PPAR γ ampliamente establecida se ha encontrado que juega un papel central al iniciar y regular la diferenciación de adiposito [*Endocrinology* 135,798-800, (1994)] y la homeostasis de energía, [*Cell*, 83,803-812 (1995); *Cell*, 99,239-242 (1999)]. Los agonistas de PPAR α estimularían la diferenciación terminal de los precursores de adiposito y originan

características de cambio morfológico y molecular de una etapa más diferenciada, menos maligna. Durante la diferenciación del adiposito, son inducidas varias proteínas altamente especializadas, que están involucradas en el almacenamiento y el metabolismo de lípidos. Se acepta que la activación del PPAR γ conduce a la expresión del gen CAP [Cell Biology, 95,14751- 14756, (1998)], sin embargo, el enlace exacto de la activación del PPAR γ a los cambios en el metabolismo de la glucosa y la disminución a la resistencia a la insulina en el músculo no ha sido clara. El PPAR α está involucrado en estimular la β oxidación de los ácidos grasos [Trends Endocrine. Metabolism, 4, 291-296 (1993)], que resultan en la reducción de los ácidos grasos libres circulantes en el plasma [Current Biol., 5,618-621 (1995)]. El papel de los PPARs en la regulación de la sensibilidad de la insulina relacionada con la obesidad y la inflamación [Int. J. Obes Relat Metab Disord. Dec; 27 Suppl 3: S17- 21 (2003)], el ° de lípidos y la sensibilidad de la insulina [Diabetes Feb; 53 Suppl 1: S43-50 (2004)] ha sido claramente bien establecida. Los PPAR también se cree que juegan un papel en enfermedades asociadas con el síndrome metabólico [Curr Top Med Chem., 3 (14): 1649-61 (2003)]. Existe evidencia creciente de que los agonistas de PPAR también pueden influenciar el sistema cardiovascular a través de las receptores PPAR así como también directamente al modular la función de la pared de los vasos [Diabetes Metab., Feb ; 30

(1): 7-12 (2004); *Drugs Today (Barc)*, Dec; 39 (12): 949-60 (2003)].

Los agonistas PPAR se han encontrado útiles en el tratamiento de la obesidad [WO 97/36579; *NatMed.*, Apr; 10 (4): 355-61 (2004)]. Los agonistas de PPAR α y γ dobles se han sugerido como útiles para el síndrome X (WO 97/25042). Los agonistas de PPAR γ y los inhibidores de reductasa HMG-CoA han exhibido sinergia e indicaron la utilidad de la combinación en el tratamiento de aterosclerosis y xantoma [EP 0753 298; *Cardiol Rev.* May-Jun; 12 (3): 158-70 (2004)].

La leptina es una proteína cuando se une a los receptores de leptina está involucrada en enviar señales de saciedad al hipotálamo. La resistencia a la leptina por lo tanto conduciría a un exceso de toma de alimento, gasto de energía reducido, obesidad, tolerancia afectada a la glucosa, y diabetes [*Science*, 269,543-46 (1995); *Recent Prog Horm Res.*, 59: 169-205 (2004); *Ann N Y Acad Sci*, Jun; 967: 363-78 (2002)]. Se ha reportado que los sensibilizadores de la insulina disminuyen la concentración de leptina en el plasma [*Proc. Natl. Acad. Sci.* 93,5793-5796 (1996); WO 98/02159].

Los compuestos heterocíclicos novedosos que son agonistas PPAR α selectivos se han reportado en la US 2003/0166697 A1 que tiene la fórmula general mencionada adelante que se incorpora aquí como referencia.

b

R^1 -Het-D-E

en donde

R^1 es un grupo heterocíclico aromático arilo opcionalmente sustituido o grupo cicloalquilo; Het es un grupo heterocíclico divalente opcionalmente sustituido; D es un alquilenos, alquenileno, alquinileno o un grupo de la fórmula

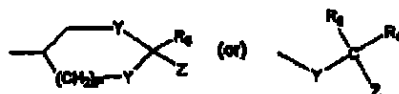


en donde W es CH o nitrógeno;

m es 1-10;

n es 0-9, con la condición de que $m+n$ es 1-10; y

E es un grupo de fórmula



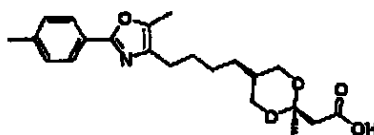
en donde Y es O o S;

R_3 y R_4 son iguales o diferentes y cada uno es H o alquilo;

p es 0-2;

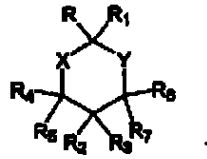
Z es carboxi, alcóxicarbonilo, hidroximetilo, carbamoilo etc.

Los compuestos representativos tienen la siguiente estructura:



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La WO 2000004011 describe compuestos que tienen la siguiente fórmula general para el tratamiento de dislipidemia, aterosclerosis y diabetes;



en donde X, Y = CH₂, O, S, NR_a (R_a = H, alquilo, arilo, etc.); R = H, alquilo, cicloalquilo, etc.; R¹ = H, alquilo, hidroxialquilo, -(CH₂)_t-COOR_c donde t = 0-6 & R_c representa H o el grupo alquilo, etc.; R₂ & R₃ = H, alquilo, cicloalquilo, arilo (C₆-C₁₀), arilo (C₆-C₁₀) alquilo (C₁-C₇), un grupo heterocíclico opcionalmente sustituido de 3-10 miembros etc.; o R₂ & R₃ opcionalmente forman una cadena -(CH₂)_{r1} (r1 = 2-5), etc.; R₄-R₇ = H, alquilo, arilo (no) sustituido, etc.

Sin embargo, el potencial terapéutico de estos compuestos para tratar las enfermedades no ha sido probado y así subsiste la necesidad de desarrollar medicinas más nuevas que sean mejores o de eficacia comparable con las regímenes de tratamiento presentes, que tengan menos efectos colaterales y requieran menos régimen de dosis.

RESUMEN DE LA INVENCION

El objetivo de esta invención es desarrollar compuestos novedosos representados por la fórmula (I) utilizados como

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agentes hipocolesterolémicos, hipolipidémicos, hipolipoproteínemicos, anti-obesidad y antihiperglicémicos que pueden tener efectos de disminución adicional del peso del cuerpo y efectos benéficos en el tratamiento y/o profilaxis de enfermedades originadas por la hiperlipidemia, enfermedades clasificadas bajo el síndrome X y la aterosclerosis.

OBJETOS DE LA INVENCION

El objeto principal de la presente invención es suministrar compuestos novedosos representados por la fórmula general (I), sus formas tautoméricas, sus sales farmacéuticamente aceptables, sus solvatos farmacéuticamente aceptables, y las composiciones farmacéuticas que los contienen y sus mezclas de estos.

Aun otro objeto de esta invención es suministrar un proceso para la preparación de compuestos novedosos representados por la fórmula general (I), sus formas tautoméricas, sus sales farmacéuticamente aceptables, sus solvatos farmacéuticamente aceptables.

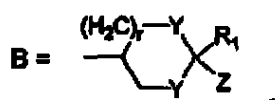
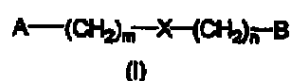
Aun otro objeto de la presente invención es suministrar composiciones farmacéuticas que contienen los compuestos de fórmula general (I), sus formas tautoméricas, sus sales farmacéuticamente aceptables, sus solvatos farmacéuticamente

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aceptables, o sus mezclas en combinación con sus vehículos, solventes, diluyentes y otros medios normalmente empleados adecuados para preparar dichas composiciones.

DESCRIPCIÓN DETALLADA DE LA INVENCION

De acuerdo con esto, la presente invención se relaciona con compuestos de la fórmula general (I),



en donde 'A' representa un grupo arilo, cicloalquilo simple o fusionado opcionalmente sustituido, o un grupo heteroarilo opcionalmente sustituido o heterociclilo opcionalmente sustituido;

'm' = 0-2 ; 'n' = 3-6;

'X' representa O, S, -N-(Ra)- o -CH₂-;

Ra representa hidrógeno, un grupo alquilo, acilo o arilo, aralquilo sustituido o no sustituido, lineal o ramificado;

'Y' en cada ocurrencia independientemente representa O o S;

R₁ representa H, alquilo sustituido o no sustituido lineal o ramificado;

r = 0-2;

Z representa

-(CH₂)_sCOOH, alcoxycarbonilo, hidroximetilo, -CN, tetrazoles sustituido o no sustituido, grupos alquilcarbonilo, s = 0-4;

Cuando 'A' es sustituido, las sustituciones adecuadas sobre 'A' se pueden seleccionar de hidroxilo, oxo, halo, tio, nitro, amino, ciano, formilo, o grupos sustituidos o no sustituidos seleccionados de amidino, alquilo, haloalquilo, perhaloalquilo, alcoxi, haloalcoxi, perhaloalcoxi, alquenoilo, alquinilo, cicloalquilo, cicloalquenoilo, bicicloalquilo, bicicloalquenoilo, alcoxi, alquenoxi, cicloalcoxi, arilo, ariloxi, aralquilo, aralcoxi, acilo, aciloxi, acilamino, amino monosustituido o disustituido, arilamino, aralquilamino, ácido carboxílico y sus derivados tales como ésteres y amidas, carbonilamino, hidroxialquilo, aminoalquilo, alcoxialquilo, ariloxialquilo, aralcoxialquilo, alquiltio, tioalquilo, ariltio, alquilsulfonilamino, alquilsulfoniloxi, alcoxicarbonilamino, ariloxicarbonilamino, aralquiloalcoxicarbonilamino, aminocarbonilamino, alquilaminocarbonilamino, alcoxiamino, hidroxilamino, derivados de sulfenilo, derivados de sulfonilo, con la condición de que cuando $X = CH_2$ y

- i) 'A' representa un grupo heterocíclico sustituido, las sustituciones sobre 'A' no representan un grupo arilo, aromático, heterocíclico o cicloalquilo; y
- ii) 'A' representa un grupo arilo sustituido, el sustituyente sobre 'A' representa un grupo alquilsulfoniloxi, ariloxi, aralcoxi, cicloalquilo, heteroarilo o heterocíclico.

Las sustituciones adecuadas sobre 'B' se pueden seleccionar de hidroxilo, oxo, halo, tio, nitro, amino, ciano, formilo, o grupos sustituidos o no sustituidos seleccionados de alquilo, haloalquilo, o grupos arilo.

Las sustituciones adecuadas de cualquiera de los sustituyentes 'A' & 'B' se pueden seleccionar de hidroxilo, oxo, halo, tio, nitro, amino, ciano, formilo, o grupos sustituidos o no sustituidos seleccionados de amidino, alquilo, haloalquilo, perhaloalquilo, alcoxi, haloalcoxi, perhaloalcoxi, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, bicicloalquilo, bicicloalquenilo, alcoxi, alquenoxi, cicloalcoxi, acilo, aciloxi, acilamino, amino monosustituido o disustituido, arilamino, aralquilamino, ácido carboxílico y sus derivados tales como ésteres y amidas, carbonilamino, hidroxialquilo, aminoalquilo, alcoxicarbonilamino, ariloxicarbonilamino, aralquiloxicarbonilamino, aminocarbonilamino, alquilaminocarbonilamino, alcoxiamino, y grupos hidroxilamino.

El término "sustituido" utilizado solo o en combinación con otros radicales, denota sustituyentes adecuados sobre el radical tal como alquilo sustituido, alquenilo sustituido, alquinilo sustituido, cicloalquilo sustituido, arilo sustituido, etc, mencionados en cualquier parte en la

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especificación. Los sustituyentes adecuados incluyen, pero no están limitados a los siguientes radicales, solos o en combinación con otros radicales tales como hidroxilo, oxo, halo, tio, nitro, amino, ciano, formilo, amidino, alquilo, haloalquilo, perhaloalquilo, alcoxi, haloalcoxi, perhaloalcoxi, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, bicicloalquilo, bicicloalquenilo, alcoxi, alquenoxi, cicloalcoxi, acilo, aciloxi, acilamino, amino monosustituido o disustituido, arilamino, aralquilamino, ácido carboxílico y sus derivados tales como ésteres y amidas, carbonilamino, hidroxialquilo, aminoalquilo, alcóxialquilo, alcóxicarbonilamino, ariloxicarbonilamino, aralquiloxicarbonilamino, ácido sulfónico y sus derivados.

Los varios grupos, radicales y sustituyentes utilizados en cualquier parte en la especificación se describe en los siguientes párrafos.

El término "alquilo" utilizado aquí, solo o en combinación con otros radicales, denota un radical lineal o ramificado que contiene uno o doce carbonos, tales como metilo, etilo, *n*-propilo, iso-propilo, *n*-butilo, sec-butilo, tert-butilo, amilo, t-amilo, *n*-pentilo, *n*-hexilo, iso-hexilo, heptilo, octilo y similares.

El término "alquenilo" utilizado aquí, solo o en combinación con otros radicales, denota un radical lineal o



ramificado que contiene dos a doce carbonos tales como vinilo, alilo, 2-butenilo, 3-butenilo, 2-pentenilo, 3-pentenilo, 4-pentenilo, 2-hexenilo, 3-hexenilo, 4-hexenilo, 5-hexenilo, 2-heptenilo, 3-heptenilo, 4-heptenilo, 5-heptenilo, 6-heptenilo y similares. El término "alquenilo" incluye dienos y trienos de cadenas recta y ramificada.

El término "alquinilo" utilizado aquí, solo o en combinación con otros radicales, denota un radical lineal o ramificado que contiene dos a doce carbonos, tales como etinilo, 1-propinilo, 2-propinilo, 1-butinilo, 2-butinilo, 3-butinilo, 1-pentinilo, 2-pentinilo, 3-pentinilo, 4-pentinilo, 1-hexinilo, 3-hexinilo, 4-hexinilo, 5-hexinilo, y similares. El término "alquinilo" incluye di- y tri-inos.

El término "cicloalquilo" utilizado aquí, solo o en combinación con otros radicales, denota un radical que contiene tres o siete carbonos, tales como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo y similares.

El término "cicloalquenilo" utilizado aquí, solo o en combinación con otros radicales, denota un radical que contiene tres a siete carbonos, tales como ciclopropenilo, 1-ciclobutenilo, 2-ciclobutenilo, 1-ciclopentenilo, 2-ciclopentenilo, 3-ciclopentenilo, 1-ciclohexenilo, 2-

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ciclohexenilo, 3-ciclohexenilo, 1-cicloheptenilo, cicloheptadienilo, cicloheptatrienilo, y similares.

El término "alcoxi" utilizado aquí, solo o en combinación con otros radicales, denota un radical alquilo, como se definió anteriormente, unido directamente a un átomo de oxígeno, tal como metoxi, etoxi, *n*-propoxi, *iso*-propoxi, *n*-butoxi, *t*-butoxi, *iso*-butoxi, pentiloxi, hexiloxi, y similares.

El término "alquenoxi" utilizado aquí, solo o en combinación con otros radicales, denota un radical alquenilo, como se definió anteriormente, unido a un átomo de oxígeno, tal como viniloxi, aliloxi, butenoxi, pentenoxi, hexenoxi, y similares.

El término "cicloalcoxi" utilizado aquí, solo o en combinación con otros radicales, denota un radical cicloalquilo como se definió anteriormente, unido directamente a un átomo de oxígeno, tal como ciclopropiloxi, ciclobutiloxi, ciclopentiloxi, ciclohexiloxi, cicloheptiloxi y similares.

El término "halo" o "halógeno" utilizado aquí, solo o en combinación con otros radicales, tal como "haloalquilo", "perhaloalquilo" etc. se refiere a los grupos flúor, cloro, bromo o yodo.

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El término "haloalquilo" denota un radical alquilo, como se definió anteriormente, sustituido con uno o más halógenos; tal como perhaloalquilo, más preferiblemente, perfluoroalquilo (C1-C6) tal como fluorometilo, difluorometilo, trifluorometilo, fluoroetilo, difluoroetilo, trifluoroetilo, metilo mono o polihalo sustituido, etilo, propilo, butilo, pentilo o grupos hexilo. El término "haloalcoxi" denota un haloalquilo, como se definió anteriormente, directamente unido a un átomo de oxígeno, tales como los grupos fluorometoxi, clorometoxi, fluoroetoxi cloroetoxi, y similares. El término "perhaloalcoxi" denota un radical perhaloalquilo, como se definió anteriormente, directamente unido a un átomo de oxígeno, trifluorometoxi, trifluoroetoxi, y similares.

El término "arilo" o "aromático" utilizado aquí, bien sea solo o en combinación con otros radicales, denota un sistema aromático que contiene uno, dos o tres anillos, en donde tales anillos se pueden unir juntos de una manera pendiente o se pueden fusionar, tal como fenilo, naftilo, tetrahidronaftilo, indano, bifenilo, y similares. El término "aralquilo" denota un grupo alquilo, como se definió anteriormente, unido a un arilo, tal como bencilo, fenetilo, naftilmetilo, y similares. El término "ariloxi" denota un radical arilo, como se definió anteriormente, unido a un grupo alcoxi, tal como fenoxi, naftiloxi y similares, que

pueden ser sustituidos. El término "aralcoxi" denota una porción arilalquilo, como se definió anteriormente, tal como benciloxi, fenetiloxi, naftilmetiloxi, fenilpropiloxi, y similares, que pueden ser sustituidos.

El término "heterociclilo" o "heterocíclico" utilizado aquí, bien sea solo o en combinación con otros radicales, denota radicales en forma de anillo saturados, parcialmente saturados o insaturados, los heteroátomos seleccionados de nitrógeno, azufre y oxígeno. Ejemplos de radicales heterocíclicos saturados incluyen aziridinilo, azetidínilo, pirrolidinilo, imidazolidinilo, piperidinilo, piperazinilo, 2-oxopiperidinilo, 4-oxopiperidinilo, 2-oxopiperazinilo, 3-oxopiperazinilo, morfolinilo, tiomorfolinilo, 2-oxomorfolinilo, azepínilo, diazepínilo, oxapínilo, tiazepínilo, oxazolidinilo, tiazolidinilo, y similares; ejemplos de radicales parcialmente saturados incluyen dihidrotiofeno, dihidropirano, dihidrofurano, dihidrotiazol, y similares.

El término "heteroarilo" o "heteroaromático" utilizado aquí, bien sea solo o en combinación con otros radicales, denota radicales heterocíclicos de 5-6 miembros insaturados que contienen uno o más heteroátomos seleccionados de O, N o S, tal como piridilo, tienilo, furilo, pirrolilo, oxazolilo, tiazolilo, isotiazolilo, imidazolilo, isoxazolilo, oxadiazolilo, tiadiazolilo, triazolilo, tetrazolilo,

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benzopiraniilo, benzopiranonilo, benzofuraniilo, benzotienilo, indolinilo, indolilo, azaindolilo, azaindolinilo, benzodihidrofuraniilo, benzodihidrotienilo, pirazolopirimidinilo, pirazolopirimidonilo, azaquinazolinilo, azaquinazolinoilo, piridofuraniilo, piridotienilo, tienopirimidilo, tienopirimidonilo, quinolinilo, pirimidinilo, pirazolilo, quinazolinilo, quinazolonilo, pirimidonilo, piridazinilo, triazinilo, benzoxazinilo, benzoxazinonilo, benzotiazinilo, benzotiazinonilo, benzoxazolilo, benzotiazolilo, bencimidazolilo, benzotriazolilo, ftalazinilo, naftilidinilo, purinilo, carbazolilo, fenotiazinilo, fenoxazinilo, y similares.

El término "acilo" utilizado aquí, bien sea solo o en combinación con otros radicales, denota un radical que contiene uno a ocho carbonos tal como formilo, acetilo, propanoilo, butanoilo, iso-butanoilo, pentanoilo, hexanoilo, heptanoilo, benzoilo y similares, que pueden ser sustituidos.

El término "aciloxi" utilizado aquí, bien sea solo o en combinación con otros radicales, denota un radical acilo, como se definió anteriormente, directamente unido a un átomo de oxígeno, tal como acetiloxi, propioniloxi, butanoiloxi, iso-butanoiloxi, benzoiloxi y similares.

El término "acilamino" utilizado aquí, bien sea solo o en combinación con otros radicales, denota un grupo acilo

como se definió anteriormente, puede ser CH_3CONH , $\text{C}_2\text{H}_5\text{CONH}$, $\text{C}_3\text{H}_7\text{CONH}$, $\text{C}_4\text{H}_9\text{CONH}$, $\text{C}_6\text{H}_5\text{CONH}$ y similares, que pueden ser sustituidos.

El término "amino mono-sustituido" utilizado aquí, bien sea solo o en combinación con otros radicales, denota un grupo amino, sustituido con un grupo seleccionados de alquilo ($\text{C}_1\text{-C}_6$), alquilo sustituido, arilo, arilo sustituido o grupos arilalquilo. Ejemplos de grupo monoalquilamino incluye metilamina, etilamina, *n*-propilamina, *n*-butilamina, *n*-pentilamina y similares.

El término "amino disustituido" utilizado aquí, bien sea solo o en combinación con otros radicales, denota un grupo amino, sustituidos con dos radicales que pueden ser iguales o diferentes seleccionados de alquilo ($\text{C}_1\text{-C}_6$), alquilo sustituido, arilo, substituido, o grupos arilalquilo, tal como dimetilamino, metiletilamino, dietilamino, fenilmetilamino y similares.

El término "arilamino" utilizado aquí, bien sea solo o en combinación con otros radicales, denota un grupo arilo, como se definió anteriormente, ligado a través amino que tiene una valencia libre unida desde el átomo de nitrógeno, tal como fenilamino, naftilamino, *n*-metil anilino y similares.

El término "aralquilamino" utilizado aquí, bien sea solo o en combinación con otros radicales, denota un grupo arilalquilo se definió anteriormente ligado a través de amino que tiene una valencia libre unida desde el átomo de nitrógeno por ejemplo bencilamino, fenetilamino, 3-fenilpropilamino, 1-naftilmetilamino, 2-(1-naftil)etilamino y similares.

El término "oxo" o "carbonilo" utilizado aquí, denota solo ($-C=O-$) o en combinación con otros radicales, tal como "alquilcarbonilo", denota un radical carbonilo ($-C=O-$) sustituido con un radical alquilo tal como acilo o alcanilo, como se describió anteriormente.

El término "ácido carboxílico" utilizado aquí, solo o en combinación con otros radicales, denota un grupo $-COH$, e incluye derivados de ácido carboxílico tal como ésteres y amidas. El término "éster" utilizado aquí, solo o en combinación con otros radicales, denota un grupo $-COO-$, e incluye derivados de ácido carboxílico, en donde las porciones éster son alcóxicarbonilo, tal como metóxicarbonilo, etóxicarbonilo, y similares, que pueden ser sustituidos; grupo arilóxicarbonilo tal como fenóxicarbonilo, naftilóxicarbonilo, y similares, que pueden ser sustituidos; grupo aralcóxicarbonilo tal como bencilóxicarbonilo, fenetilóxicarbonilo, naftilmetoxycarbonilo, y similares, que pueden ser sustituidos.

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El término "amida" utilizado aquí, solo o en combinación con otros radicales, representa un radical aminocarbonilo ($\text{H}_2\text{N}-\text{C}=\text{O}-$), en donde el grupo amino es mono- o di-sustituido o no sustituido, tal como metilamida, dimetilamida, etilamida, dietilamida, y similares. El término "aminocarbonilo" utilizado aquí, bien sea solo o en combinación con otros radicales, con otros términos tales como "aminocarbonilalquilo", "n-alquilaminocarbonilo", "N-arilaminocarbonilo", "N,N-dialquilaminocarbonilo", "N-alquil-N-arilaminocarbonilo", "N-alquil-N-hidroxiaminocarbonilo", y "N-alquil-N-hidroxiaminocarbonilalquilo", sustituido o no sustituido. Los términos "N-alquilaminocarbonilo" y "N,N-dialquilaminocarbonilo" denota radicales aminocarbonilo, como se definió anteriormente, que han sido sustituidos con un radical alquilo y con dos radicales alquilo, respectivamente. Preferidos son "alquilaminocarbonilo inferior" que tienen radicales alquilo inferior como se describió anteriormente unidos al radical aminocarbonilo. Los términos "N-arilaminocarbonilo" y "N-alquil-N-arilaminocarbonilo" denota radicales aminocarbonilo sustituidos, respectivamente, con un radical arilo, o un alquilo, y un radical arilo. El término "aminocarbonilalquilo" incluye radicales alquilo sustituidos con radicales aminocarbonilo.

El término "hidroxialquilo" utilizado aquí, bien sea solo o en combinación con otros radicales, denota un grupo

alquilo, como se definió anteriormente, sustituidos con uno o más radicales hidroxilo, tal como hidroximetilo, hidroxietilo, hidroxipropilo, hidroxibutilo, hidroxipentilo, hidroxihexilo y similares.

El término "aminoalquilo" utilizado aquí, solo o en combinación con otros radicales, denota una porción amino ($-NH_2$) unida a un radical alquilo, como se definió anteriormente, que pueden ser sustituidos, tal como aminoalquilo mono- y di-sustituido. El término "alquilamino" utilizado aquí, solo o en combinación con otros radicales, denota un radical alquilo, como se definió anteriormente, unido a un grupo amino, que puede ser sustituido, tal como alquilamino mono- y di-sustituido.

El término "alcoxialquilo" utilizado aquí, solo o en combinación con otros radicales, denota un grupo alcoxi, como se definió anteriormente, unido a un grupo alquilo, tal como metoximetilo, etoximetilo, metoxietilo, etoxietilo y similares. El término "ariloxialquilo" utilizado aquí, solo o en combinación con otros radicales, incluye fenoximetilo, naftiloximetilo, y similares. El término "aralcoxialquilo" utilizado aquí, solo o en combinación con otros radicales, incluye $C_6H_5CH_2OCH_2$, $C_6H_5CH_2OCH_2CH_2$, y similares.

El término "alquiltio" utilizado aquí, bien sea solo o en combinación con otros radicales, denota un sustituyente

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monovalente recto o ramificado o cíclico que comprende un grupo alquilo de uno a doce átomos de carbono, como se definió anteriormente, ligado a través de un átomo de azufre divalente que tiene una valencia libre unida desde el átomo de azufre, tal como metiltio, etiltio, propiltio, butiltio, pentiltio y similares. Ejemplos de alquiltio cíclico son ciclopropiltio, ciclobutiltio, ciclopentiltio, ciclohexiltio y similares, que pueden ser sustituidos.

El término "tioalquilo" utilizado aquí, bien sea solo o en combinación con otros radicales, denota un grupo alquilo, como se definió anteriormente, unidos a un grupo de fórmula -SR', en donde R' representa hidrógeno, un grupo alquilo o arilo, por ejemplo tiometilo, metiltiometilo, feniltiometilo y similares, que pueden ser sustituidos.

El término "ariltio" utilizado aquí, bien sea solo o en combinación con otros radicales, denota un grupo arilo, como se definió anteriormente, ligado a través un átomo de azufre divalente, que tiene un enlace de valencia libre desde el átomo de azufre tal como feniltio, naftiltio y similares.

El término "alcoxycarbonilamino" utilizado aquí, solo o en combinación con otros radicales, denota un grupo alcoxycarbonilo, como se definió anteriormente, unido a un grupo amino, tal como metoxycarbonilamino, etoxycarbonilamino, y similares. El término

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"ariloxycarbonilamino" utilizado aquí, solo o en combinación con otros radicales, denota un grupo ariloxycarbonilo, como se definió anteriormente, unidos a un grupo amino, tal como C_6H_5OCONH , $C_6H_5OCONCH_3$, $C_6H_5OCONC_2H_5$, $C_6H_4(CH_3O)CONH$, $C_6H_4(OCH_3)OCONH$, y similares. El término "aralcoxicarbonilamino" utilizado aquí, solo o en combinación con otros radicales, denota un grupo aralcoxicarbonilo, como se definió anteriormente, unido a un grupo amino $C_6H_5CH_2OCONH$, $C_6H_5CH_2CH_2CH_2OCONH$, $C_6H_5CH_2OCONHCH_3$, $C_6H_5CH_2OCONC_2H_5$, $C_6H_4(CH_3)CH_2OCONH$, $C_6H_4(OCH_3)CH_2OCONH$, y similares.

El término "aminocarbonilamino", "alquilaminocarbonilamino", "dialquilaminocarbonilamino" utilizado aquí, solo o en combinación con otros radicales, denota un grupo carbonilamino ($-CONH_2$), unido a un amino (NH_2), un grupo alquilamino o un grupo dialquilamino respectivamente, en donde el grupo alquilo es como se definió anteriormente.

El término "amidino" utilizado aquí, bien sea solo o en combinación con otros radicales, denota un radical $-C(=NH)-NH_2$. El término "alquilamidino" denota un radical alquilo, como se discutió anteriormente, unido a un grupo amidino.

El término "alcoxiamino" utilizado aquí, solo o en combinación con otros radicales, denota un grupo alcoxi, como se definió anteriormente, unido a un grupo amino. El término

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"hidroxiamino" utilizado aquí, solo o en combinación con otros radicales, denota una porción -NHOH y puede ser sustituido.

El término "sulfenilo" o "sulfenilo y sus derivados" utilizado aquí, solo o en combinación con otros radicales, denota un grupo bivalente, -SO- o R_xSO , en donde R_x es alquilo sustituido o no sustituido, arilo, heteroarilo, heterociclilo, y similares.

El término "sulfonilo" o "sulfonas y sus derivados" utilizado aquí, bien sea solo o en combinación con otros radicales, con otros términos tal como alquilsulfonilo, denota radical bivalente $\text{-SO}_2\text{-}$, o $\text{R}_x\text{SO}_2\text{-}$, en donde R_x son grupos sustituidos o no sustituidos seleccionados de alquilo, arilo, heteroarilo, heterociclilo, y similares. "Alquilsulfonilo" denota radicales alquilo, como se definió anteriormente, unidos a un radical sulfonilo, tal como metilsulfonilo, etilsulfonilo, propilsulfonilo y similares. El término "arilsulfonilo" utilizado aquí, bien sea solo o en combinación con otros radicales, denota radicales arilo, como se definió anteriormente, unidos a un radical sulfonilo, tal como fenilsulfonilo y similares.

Los grupos adecuados y sustituyentes sobre los grupos pueden ser seleccionados de aquellos descritos en cualquier parte en la especificación.

SC

Los compuestos particularmente útiles se pueden seleccionar de

Metil-5-[4-(2-etil-4-oxo-4H-quinazolin-3-il)-butil]-2-metil-[1,3]dioxano-2-carboxilato;

Metil-5-[4-(2-etil-quinazolin-4-iloxi)-butil]-2-metil-[1,3]dioxano-2-carboxilato;

Metil-5-[6-(4-cloro-fenil)-5-(4-metilsulfanil-fenil)-6-oxo-hexil]-2-metil-[1,3]dioxano-2-carboxilato;

Metil-5-[4-(2,3-dihidro-benzo[1,4]oxazin-4-il)-butil]-2-metil-[1,3]dioxano-2-carboxilato;

Metil-2-metil-5-(4-fenoxazin-10-il-butil)-[1,3]dioxano-2-carboxilato;

Metil-5-[4-(6,7-dihidro-4H-tieno[3,2-c]piridin-5-il)-butil]-2-metil-[1,3]dioxano-2-carboxilato;

Metil-5-(4-carbazol-9-il-butil)-2-metil-[1,3]dioxano-2-carboxilato;

Metil-2-metil-5-[4-(3-oxo-2,3-dihidro-benzo[1,4]tiazin-4-il)-butil]-[1,3]dioxano-2-carboxilato;

Metil-5-[4-(2,3-dihidro-benzo[1,4]tiazin-4-il)-butil]-2-metil-[1,3]dioxano-2-carboxilato;

Metil-2-metil-5-(4-fenotiazin-10-il-butil)-[1,3]dioxano-2-carboxilato;

Metil-5-(4-indol-1-il-butil)-2-metil-[1,3]dioxano-2-carboxilato ;

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Metil-2-metil-5-(5-fenil-5-piridin-4-il-pentil)-[1,3]dioxano-2-carboxilato;

Metil-5-[4-(4-bencil-fenoxi)-butil]-2-metil-[1,3]dioxano-2-carboxilato ;

Metil-2-metil-5-[4-(3-oxo-2,3-dihidro-benzo[1,4]oxazin-4-il)-butil]-[1,3]dioxano-2-carboxilato;

Metil-5-[4-[2-(2-hidroxi-etil)-3-oxo-2,3-dihidro-benzo[1,4]oxazin-4-il]-butil]-2-metil-[1,3]dioxano-2-carboxilato;

Metil-2-metil-5-[4-(4-fenoxi-fenoxi)-butil]-[1,3]dioxano-2-carboxilato;

Metil-5-(3-benzo[1,3]dioxol-5-il-propil)-2-metil-[1,3]dioxano-2-carboxilato ;

Metil-5-[4-(4-metanosulfoniloxi-fenil)-butil]-2-metil-[1,3]dioxano-2-carboxilato;

Metil-5-[4-(4-benciloxi-fenil)-butil]-2-metil-[1,3]dioxano-2-carboxilato ;

Metil-2-metil-5-(3-fenilsulfanil-propil)-[1,3]dioxano-2-carboxilato;

Etil-5-[3-(4-bromo-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxilato;

Metil-2-metil-5-[3-(4-fenoxi-fenoxi)-propil]-[1,3]dioxano-2-carboxilato;

Metil-5-[3-(4-isopropil-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxilato ;

Metil-2-metil-5-(3-p-toliloxi-propil)-[1,3]dioxano-2-carboxilato;

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Metil-5-[3-(4-bromo-fenilsulfanil)-propil]-2-metil-[1,3]dioxano-2-carboxilato;

Metil-2-metil-5-(3-fenoxi-propil)-[1,3]dioxano-2-carboxilato;

Metil-5-[3-(4-fluoro-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxilato;

Metil-2-metil-5-[3-(naftalen-2-iloxi)-propil]-[1,3]dioxano-2-carboxilato;

Metil-5-[3-(4-benciloxi-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxilato;

Metil-5-[3-(4-metoxi-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxilato;

Metil-5-[3-(4-bencil-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxilato;

Ácido 5-[4-(2-Etil-4-oxo-4H-quinazolin-3-il)-butil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[4-(2-Etil-quinazolin-4-iloxi)-butil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[6-(4-Cloro-fenil)-5-(4-metilsulfanil-fenil)-6-oxo-hexil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[4-(2,3-Dihidro-benzo[1,4]oxazin-4-il)-butil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-(4-fenoxazin-10-il-butil)-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;



Ácido 5-(4-Carbazol-9-il-butil)-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-[4-(3-oxo-2,3-dihidro-benzo[1,4]tiazin-4-il)-butil]-[1,3]dioxano-2-ácido carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[4-(2,3-Dihidro-benzo[1,4]tiazin-4-il)-butil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-(4-fenotiazin-10-il-butil)-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-(4-Indol-1-il-butil)-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-(5-fenil-5-piridin-4-il-pentil)-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[4-(4-Bencil-fenoxi)-butil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-[4-(3-oxo-2,3-dihidro-benzo[1,4]oxazin-4-il)-butil]-[1,3]dioxano-2-ácido carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[4-[2-(2-Hidroxi-etil)-3-oxo-2,3-dihidro-benzo[1,4]oxazin-4-il]-butil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-[4-(4-fenoxi-fenoxi)-butil]-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-(3-Benzo[1,3]dioxol-5-il-propil)-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

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Ácido 5-[4-(4-Metanosulfoniloxi-fenil)-butil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[4-(4-Benciloxi-fenil)-butil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-(3-fenilsulfanil-propil)-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[3-(4-Bromo-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-[3-(4-fenoxi-fenoxi)-propil]-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[3-(4-Isopropil-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-(3-p-toliloxi-propil)-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[3-(4-Bromo-fenilsulfanil)-propil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-(3-fenoxi-propil)-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[3-(4-Fluoro-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-[3-(naftalen-2-iloxi)-propil]-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[3-(4-Benciloxi-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

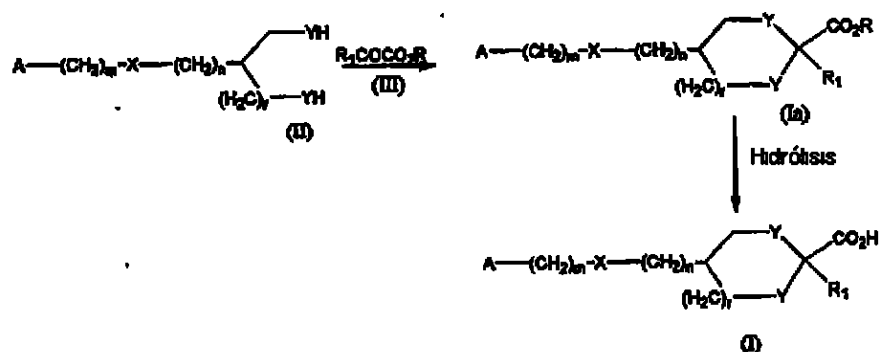
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Ácido 5-[3-(4-Metoxi-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[3-(4-Bencil-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Los compuestos novedosos de esta invención se pueden preparar utilizando las reacciones y técnicas descritas en esta sección. Las reacciones se realizan en solventes apropiados para los reactivos y materiales empleados y son adecuados para la transformación a ser efectuada. Se entenderá por aquellos expertos en la técnica que la naturaleza y el orden de las etapas sintéticas presentadas pueden ser variadas para los propósitos de optimización y formación de los compuestos de la presente invención.

Esquema 1



Los compuestos de fórmula general (I) en donde todos los símbolos son como se definió anteriormente se pueden preparar mediante la ruta subrayada en el esquema 1 anterior que comprende

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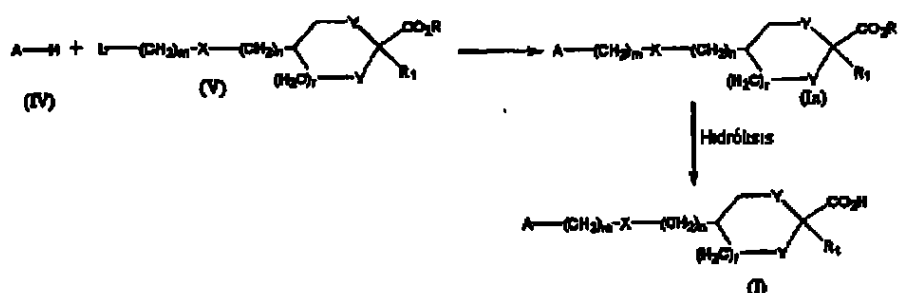
- i) Hacer reaccionar un compuesto de fórmula (II) con un compuesto de fórmula (III) para obtener un compuesto de fórmula (Ia) en donde R representa grupo alquilo y todos los otros símbolos son como se definió anteriormente. De manera general, la reacción se puede llevar a cabo en un solvente apropiado seleccionado de solventes polares tal como acetonitrilo, DMF, y similares, solventes de éter tales como THF, dioxano, dietileter, dimetoxietano y similares, solventes halogenados como CHCl_3 o diclorometano, dicloroetano y similares, solventes de hidrocarburo tales como benceno, tolueno, *n*-hexano, ciclohexano y similares, solventes de éster tal como acetato de metilo, acetato de etilo, acetato de isopropilo y similares o mezclas de estos, en la presencia de ácido Lewis tales como complejo de boro trifluoruro dietil éter a -22 a 120°C . La reacción se puede llevar a cabo en la atmósfera de un gas inerte tal como nitrógeno. El tiempo de reacción puede variar desde 30 minutos a 24 horas.
- ii) Hidrolizar un compuesto de fórmula (Ia) con reactivos/solventes adecuados a un compuesto de fórmula (I) en donde todos los símbolos son como se definió anteriormente. Los solventes hidrolizantes adecuados se pueden seleccionar de solventes alcohólicos como metanol, etanol, propanol, isopropanol, *t*-butanol y similares o mezclas de estos, y agua en la presencia de

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ácidos o bases adecuadas a -20 a 100° C. Los ácidos adecuados pueden ser HCl, PTSA y similares; las bases adecuadas pueden ser LiOH, NaOH, KOH y similares.

iii) Opcionalmente, si se desea los compuestos de fórmula (I) se convierten a sus sales farmacéuticamente aceptables adecuadas mediante técnicas conocidas en el arte.

Esquema 2



Alternativamente, los compuestos de la fórmula general (I) en donde todos los símbolos son como se definió anteriormente se pueden preparar mediante la ruta subrayada en el esquema 2 anterior que comprende;

i) Hacer reaccionar el compuesto de fórmula general (V) en donde L representa un grupo saliente adecuado tal como halógeno, mesilato, tosilato, triflato y similares, con los compuestos de fórmula general (IV) para obtener el compuesto de fórmula (Ia). Las bases adecuadas como los hidruros metálicos por ejemplo NaH y similares, carbonatos de metal alcalino por ejemplo carbonato de potasio, carbonato de sodio y similares, hidróxido de

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sodio, hidróxido de potasio, bases orgánicas, por ejemplo trialkuilaminas y similares, reactivos de organolitio por ejemplo butilitio, diisopropilamida de litio, hexametildisilazida de litio y similares se pueden utilizar. La reacción puede ser llevada a cabo en solventes adecuados como DMF, DMSO, THF, dioxano, *n*-hexano, ciclohexano, dicloroetano, acetona, diclorometano, tolueno y similares o mezclas de estos basados en la adecuabilidad para las bases utilizadas. La temperatura de reacción puede variar desde -78° C a la temperatura de reflujo de el o los solventes utilizados. La atmósfera inerte puede opcionalmente ser mantenida utilizando N₂ He o gas argón. El tiempo de reacción puede variar desde 1 a 72 horas.

- ii) Hidrolizar un compuesto de fórmula (Ia) con reactivos/solventes adecuados a un compuesto de fórmula (I) en donde todos los símbolos son como se definió anteriormente. Los solventes hidrolizantes adecuados pueden ser seleccionados de solventes alcohólicos como metanol, etanol, propanol, isopropanol, *t*-butanol y similares o mezclas de estos, y agua en la presencia de ácidos o bases adecuadas a -20 a 100° C. Los ácidos adecuados pueden ser HCl, PTSA y similares; las bases adecuadas pueden ser NaOH, KOH y similares.

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iii) Opcionalmente, si se desea los compuestos de fórmula (I) son convertidos a sus sales farmacéuticamente aceptables adecuadas mediante técnicas conocidas en el arte.

Se apreciará que cualquiera de las reacciones anteriormente mencionadas cualquier grupo reactivo en la molécula sustrato puede estar protegida, de acuerdo con práctica química convencional. Los grupos protectores adecuados en cualquiera de las reacciones anteriormente mencionadas son aquellos utilizados convencionalmente en el arte. Los métodos de formación y remoción en tales grupos protectores son aquellos métodos convencionales apropiados en la molécula que está protegida. T. W. Greene y P. G. M. Wuts "Protective groups in Organic Synthesis", John Wiley & Sons, Incos, 1999, 3rd Ed., junto con las referencias citadas allí.

Se apreciará que cuando los sustituyentes tienen sitios diferentes donde ellos se pueden unir, tal como sustituyentes diferentemente unidos también están incluidos en la presente invención.

Los compuestos novedosos de la presente invención se pueden formular en composiciones farmacéuticamente aceptables adecuadas al combinar con excipientes adecuados mediante técnicas y procesos y concentraciones que son bien conocidas.

Los compuestos de fórmula (I) o las composiciones farmacéuticas que los contienen se pueden administrar bien sea mediante administración oral, tópica o parenteral.

La composición farmacéutica se suministra al emplear técnicas convencionales. Preferiblemente la composición está en forma de dosis unitaria que contiene una cantidad efectiva del componente activo, esto es, los compuestos de fórmula (I) de acuerdo con esta invención.

La cantidad del componente activo, esto es, el compuesto de fórmula (I) de acuerdo con esta invención, y la composición farmacéutica y la forma de dosis unitaria de esta se puede variar o ajustar ampliamente dependiendo del método de aplicación particular, la potencia del compuesto particular y la concentración deseada. De manera general, la cantidad del componente activo variará entre 0.5% a 90% en peso de la composición,

Los compuestos de fórmula general (I) o las composiciones de estas son útiles para el tratamiento y/o profilaxis de enfermedades originadas por desórdenes metabólicos tales como hiperlipidemia, resistencia a la insulina, resistencia a leptina, Síndrome X, hiperglicemia, obesidad o inflamación.

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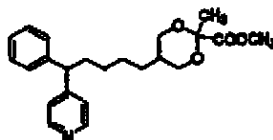
La invención se explica con mayor detalle mediante los ejemplos dados adelante, que son suministrados por vía de ilustración solamente y por lo tanto no deben ser considerados como limitantes de la invención.

Se apreciará que uno o más procesos descritos en los esquemas generales anteriores se pueden utilizar para preparar los compuestos de la presente invención.

Los datos espectrales de ^1H RMN dados en las tablas (vide infra) son registrados utilizando un espectrómetro a 300 MHz (Bruker AVANCE-300) y reportado en escala δ . Hasta que no se mencione otra cosa el solvente utilizado para el RMN es CDCl_3 , utilizando Tetrametil silano en el estándar interno.

Preparación 1

Metil-2-metil-5-(5-fenil-5-piridin-4-il-pentil)-
[1,3]dioxano-2-carboxilato (compuesto No. 12)

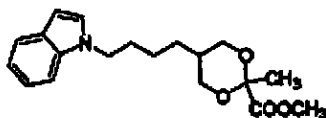


Una solución de 4-bencil piridina (250 mg) en tetrahidrofurano seco (3 mL) se enfría a -78°C y se agrega 2.35 mL de solución 1M de hexametildisilazida de litio en tetrahidrofurano. Después de agitar durante una hora a la

misma temperatura se agrega otra solución de Metil-5-(4-yodo-butyl)-2-metil-[1,3]dioxano-2-carboxilato (500 mg) en tetrahidrofurano (3 mL) y la mezcla de reacción se agita durante 3 horas permitiendo que la temperatura se eleve a 30° C. La mezcla de reacción se vierte en agua fría de hielo (25 mL) y se extrae con acetato de etilo (3 X 10 mL). El extracto orgánico combinado se lava con agua (25 mL), solución salina (25 mL), se seca sobre sulfato de sodio y se evapora bajo presión reducida. El producto crudo obtenido se cromatografía con flash sobre gel de sílice utilizando 10% de acetato de etilo en éter de petróleo como eluyente para producir 233 mg del producto.

Preparación 2

Metil-5-(4-indol-1-il-butyl)-2-metil-[1,3]dioxano-2-carboxilato (compuesto No. 11)



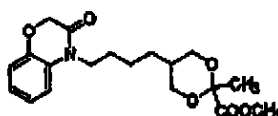
Una solución de indol (340 mg) en dimetil sulfóxido (3 mL) se agrega a una suspensión fría con hielo de hidróxido de potasio (326 mg) en dimetil sulfóxido (3 mL). Después de agitar durante 10 minutos se agrega una solución de metil-5-(4-yodo-butyl)-2-metil-[1,3]dioxano-2-carboxilato (1.0 g) en dimetil sulfóxido (5 mL) y la mezcla de reacción se agita

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durante 5 horas a 30° C. La mezcla de reacción se vierte en agua fría de hielo (50 mL) y se extrae con acetato de etilo (3 X 20 mL). El extracto orgánico combinado se lava con agua (50 mL), solución salina (50 mL), se seca sobre sulfato de sodio y se evapora bajo presión reducida. El producto crudo se cromatografía con flash sobre gel de sílice utilizando 10% de acetato de etilo en éter de petróleo como eluyente para producir 400 mg del producto.

Preparación 3

Metil-2-metil-5-[4-(3-oxo-2,3-dihidro-benzo[1,4]oxazin-4-il)-butil]-[1,3]dioxano-2-carboxilato (compuesto No. 14)



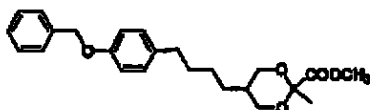
A una suspensión agitada de carbonato de cesio (1.0 g) en dimetil formamida (5 mL) se agrega una solución de 4H-benzo[1,4]oxazin-3-ona (250 mg) en dimetil formamida (3 mL) se agrega. Después de agitar en atmósfera de nitrógeno durante 30 minutos se agrega otra solución de Metil-5-(4-yodo-butyl)-2-metil-[1,3]dioxano-2-carboxilato (574 mg) en dimetil formamida (3 mL) y la mezcla de reacción se agita a temperatura ambiente durante 2 horas. La mezcla de reacción se vierte en agua fría de hielo (50 mL) y se extrae con acetato de etilo (3 X 30 mL). El extracto orgánico combinado

se lava con agua (50 mL), solución salina (50 mL), se seca sobre sulfato de sodio y se evapora bajo presión reducida. El producto crudo se cromatografía con flash sobre gel de sílice utilizando 15% de acetato de etilo en éter de petróleo como eluyente para producir 483 mg del producto.

Preparación 4

Metil 5-[4-(4-benciloxi-fenil)-butil]-2-metil-[1,3]dioxano-2-carboxilato (compuesto No. 18)

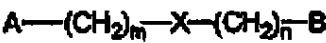
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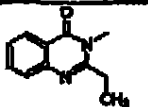
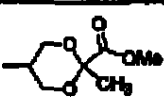
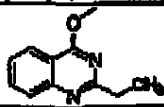
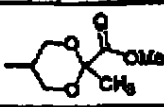
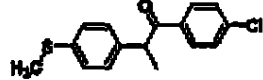
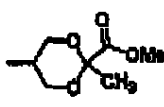


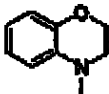
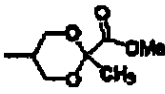
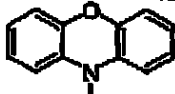
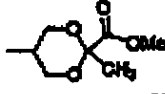
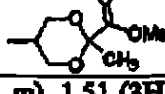
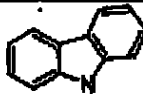
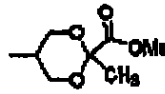
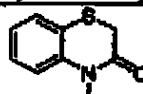
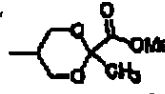
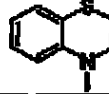
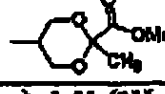
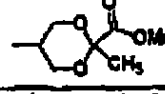
A una solución de 2-[4-(4-benciloxi-fenil)-butil]-propano-1,3-diol (1.5 g) en acetonitrilo (15 mL) se agrega metil piruvato (2.1 g) seguido por complejo de trifluoruro de boro- dietil éter al 98% (1.7 g) y la mezcla de reacción se agita a temperatura ambiente durante 18 horas. La mezcla de reacción se vierte en una solución saturada de bicarbonato de sodio (100 mL) y se extrae con acetato de etilo (3 X 50 mL). El extracto orgánico combinado se lava con agua (100 mL), solución salina (100 mL), se seca sobre sulfato de sodio y se evapora bajo presión reducida. El producto crudo se cromatografía con flash sobre gel de sílice utilizando 10% de acetato de etilo en éter de petróleo como eluyente para obtener 867 mg del producto del título.

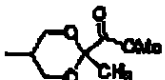
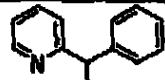
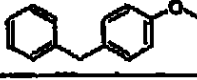
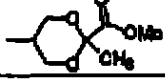
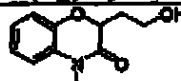
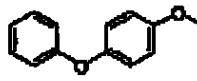
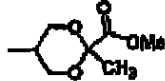
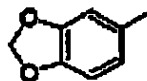
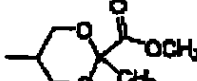
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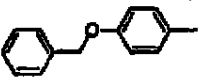
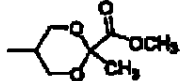
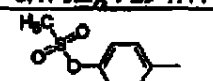
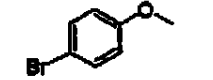
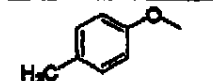
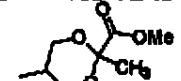
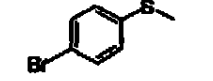
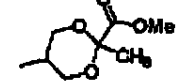
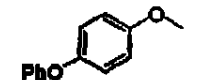
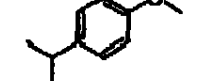
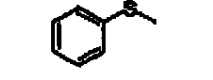
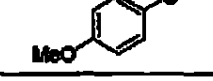
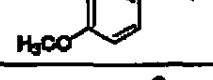
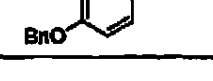
Tabla 1

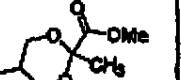
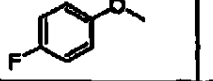
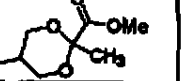
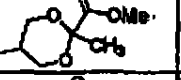
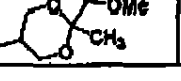


S.No.	A	B	$-(CH_2)_m-X-(CH_2)_n-$	Mol. Wt.	% Yield
1.			$(CH_2)_4$	388	60
	^1H : 1.1 (2H, m), 1.2 (2H, m), 1.4 (3H, t, J=7.3 Hz), 1.5 (3H, s), 1.7 (2H, m), 2.0 (1H, m), 2.8 (2H, q, J=7.3 Hz), 3.4 (2H, t, J=11.5 Hz), 3.8 (3H, s), 4.0 (2H, dd, J=11.8&4.5 Hz), 4.06 (2H, t, J=7.7 Hz), 7.4 (1H, t, J=7.6 Hz), 7.6 (1H, d, J=7.7 Hz), 7.7 (1H, t, J=7.0 Hz), 8.2 (1H, d, J=7.8 Hz).				
2.			$(CH_2)_4$	388	40
	^1H : 1.1 (2H, m), 1.2 (2H, m), 1.4 (3H, t, J=7.6 Hz), 1.5 (3H, s), 1.8 (2H, m), 2.0 (1H, m), 2.9 (2H, q, J=7.6 Hz), 3.4 (2H, t, J=11.5 Hz), 3.8 (3H, s), 4.0 (2H, dd, J=11.9 & 4.5 Hz), 4.5 (2H, t, J=6.5 Hz), 7.5 (1H, t, J=7.2 Hz), 7.8 (1H, t, J=7.1 Hz), 7.8 (1H, d, J=8.3 Hz), 8.1 (1H, d, J=8.0 Hz).				
3.			$(CH_2)_4$	490.5	48
	^1H : 1.0 (2H, m), 1.2 (2H, m), 1.49 (3H, s), 1.7 (2H, m), 1.9 (1H, m), 2.0 (2H, m), 2.4 (3H, s), 3.3 (2H, t, J=11.6 Hz), 3.8 (2H, s), 3.9 (2H, dd, J=11.9 & 4.56 Hz), 4.3 (1H, t, J=7.17 Hz), 7.1 (4H, m), 7.3 (2H, d, J=8.5 Hz), 7.8 (2H, d, J=8.5 Hz).				

4.			$(CH_2)_4$	349	54
	¹ H: 1.08 (2H, m), 1.3 (2H, m), 1.58 (3H, s), 1.75 (2H, m), 2.0 (2H, m), 3.2 (2H, t, J=7.5 Hz), 3.3 (2H, m), 3.4 (2H, t, J=11.6 Hz), 3.83 (3H, s), 3.96 (2H, dd, J=4.6 & 11.8 Hz), 4.22 (2H, t, J=4.3 Hz), 6.6 (2H, m), 6.8 (2H, m).				
5.			$(CH_2)_4$	397	29
	¹ H: 1.08 (2H, m), 1.36 (2H, m), 1.51 (3H, s), 1.65 (2H, m), 2.0 (2H, m), 3.4 (4H, m), 3.83 (3H, s), 3.9 (2H, dd, J=4.6 & 11.6 Hz), 6.4 (2H, d, J=7.86 Hz), 6.62 (4H, m), 6.77 (2H, m).				
6.			$(CH_2)_4$	353	77
	¹ H: 1.07 (2H, m), 1.3 (2H, m), 1.51 (3H, s), 1.6 (2H, m), 2.03 (1H, m), 2.5 (2H, d, J=7.8 Hz), 2.76 (2H, t, J=5.0 Hz), 2.8 (2H, m), 3.39 (2H, t, J=11.64 Hz), 3.54 (2H, s), 3.53 (3H, s), 3.95 (2H, m), 6.7 (1H, d, J=5.0 Hz), 7.0 (1H, d, J=5.0 Hz)				
7.			$(CH_2)_4$	381	86
	¹ H: 1.0 (2H, m), 1.3 (2H, m), 1.49 (3H, s), 1.87 (2H, m), 1.95 (1H, m), 3.4 (2H, t, J=11.63 Hz), 3.8 (3H, s), 3.89 (2H, dd, J=4.1 & 11.7 Hz), 4.3 (2H, t, J=7.0 Hz), 7.2 (2H, t, J=7.3 Hz), 7.34 (2H, d, J=8.1 Hz), 7.45 (2H, m), 8.1 (2H, d, J=7.74 Hz).				
8.			$(CH_2)_4$	379	59
	¹ H: 1.0 (2H, m), 1.28 (2H, m), 1.5 (3H, s), 1.54-1.68 (4H, m), 1.9 (1H, m), 3.36 (2H, s), 3.82 (3H, s), 3.89-4.01 (4H, m), 6.9 (2H, m), 7.2 (1H, d, J=7.2 Hz), 7.38 (1H, d, J=7.67 Hz).				
9.			$(CH_2)_4$	365	65
	¹ H: 1.0 (2H, m), 1.3 (2H, m), 1.51 (3H, s), 1.58 (2H, m), 2.0 (1H, m), 3.0 (2H, m), 3.25 (2H, t, J=7.5 Hz), 3.4 (2H, t, J=11.6 Hz), 3.6 (2H, t, J=5.0 Hz), 3.8 (3H, s), 3.94 (2H, dd, J=4.7 & 11.8 Hz), 6.6 (2H, m), 7.0 (2H, m).				
10.			$(CH_2)_4$	413	41
	¹ H: 1.0 (2H, m), 1.35 (2H, m), 1.49 (3H, s), 1.75 (2H, m), 1.98 (1H, m), 3.33 (2H, t, J=11.6 Hz), 3.81 (3H, s), 3.9 (4H, m), 6.8 (2H, d, J=8.3 Hz), 6.9 (2H, t, J=7.5 Hz), 7.1 (4H, m).				

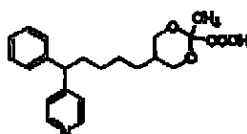
11.			$(CH_2)_4$	331	43
	¹ H: 1.0 (2H, m), 1.2 (2H, m), 1.5 (3H, s), 1.7 (2H, m), 2.0 (1H, m), 3.3 (2H, t, J=11.6 Hz), 3.8 (3H, s), 3.9 (2H, dd, J=12.0 & 4.6 Hz), 4.1 (2H, t, J=6.9 Hz), 6.5 (1H, d, J=3.0 Hz), 7.0 (1H, d, J=3.1 Hz), 7.1 (1H, d, J=7.5 Hz), 7.2 (1H, t, J=7.2 Hz), 7.3 (1H, d, J=8.2 Hz), 7.6 (1H, d, J=7.8 Hz).				
12.			$(CH_2)_4$	383	41
	¹ H: 0.93-1.0 (2H, m), 1.24 (2H, m), 1.49 (3H, s), 1.52-1.62 (2H, m), 1.95-1.99 (2H, m), 2.06 (1H, m), 3.34 (2H, t, J=11.55 Hz), 3.81 (3H, s), 3.90 (2H, q, J=11.9 & 4.5 Hz), 3.9 (1H, t, J=7.68 Hz), 7.05-7.39 (7H, m), 7.51-7.56 (1H, m), 8.55 (1H, t, J=5.04 Hz).				
13.			$(CH_2)_4$	398	98
	¹ H: 1.04-1.120 (2H, m), 1.37-1.47 (2H, m), 1.51 (3H, s), 1.68-1.80 (2H, m), 2.04 (1H, m), 3.40 (2H, t, J=11.65 Hz), 3.83 (3H, s), 3.89-3.99 (6H, m), 6.74-6.82 (2H, m), 7.04-7.10 (2H, m), 7.15-7.20 (3H, m), 7.27-7.30 (2H, m).				
14.			$(CH_2)_4$	363	80
	¹ H: 1.05-1.11 (2H, m), 1.25-1.38 (2H, m), 1.50 (3H, s), 1.58-1.71 (2H, m), 2.02 (1H, m), 3.39 (2H, t, J=11.67 Hz), 3.82 (3H, s), 3.88-3.97 (4H, m), 4.58 (2H, s), 6.92-7.04 (4H, m).				
15.			$(CH_2)_4$	407	64
	¹ H: 1.08 (2H, m), 1.34 (2H, m), 1.50 (3H, s), 1.63 (2H, m), 1.99 (1H, m), 2.19 (2H, m), 2.28 (1H, t, J=6.06 Hz), 3.40 (2H, m), 3.82 (3H, s), 3.85-4.28 (6H, m), 4.67 (1H, t, J=6.52 Hz), 6.92-7.07 (4H, m).				
16.			$(CH_2)_4$	400	98
17.			$(CH_2)_3$	322	40
	¹ H: 1.03 (2H, q, J=7.65 Hz), 1.5 (3H, s), 2.0 - 2.06 (1H, m), 2.50 (2H, t, J=7.5 Hz), 3.41 (2H, t, J=11.75 Hz), 3.49 (2H, t, J=5.13 Hz), 3.82 (3H, s), 3.82 - 3.96 (2H, dd, J=4.56 & 11.98 Hz), 5.92 (2H, s), 6.57 (1H, t, J=7.83 Hz), 6.62 (1H, s), 6.72 (1H, d, J=7.83 Hz).				

18.			(CH ₂) ₄	398	46
¹ H: 1.06 (2H, m), 1.22-1.32 (2H, m), 1.5 (3H, s), 1.59 - 1.61 (2H, m), 1.96 - 2.04 (1H, m), 2.52 (2H, t, J=7.6 Hz), 3.37 (2H, t, J=11.64 Hz), 3.82 (3H, s), 3.9 - 3.96 (2H, dd, J= 4.53 & 11.93 Hz), 5.03 (2H, s), 6.88 (2H, d, J=8.13 Hz), 7.05 (2H, d, J=8.47 Hz), 7.29-7.44 (5H, m).					
19.			(CH ₂) ₄	386	80
20.			(CH ₂) ₃	387	57
¹ H: 1.19-1.28 (2H, m), 1.34 (3H, t, J=7.11 Hz), 1.56 (3H, s), 1.71-1.76 (2H, m), 2.04-2.11 (1H, m), 3.41-3.49 (2H, m), 3.88 (2H, t, J=6.13 Hz), 3.96-3.99 (2H, m), 4.29 (2H, q, J=7.11 Hz), 6.72-6.78 (2H, m), 7.35 (2H, d, J=8.88 Hz).					
21.			(CH ₂) ₃	308	15
22.			(CH ₂) ₃	389	65
¹ H: 1.14-1.19 (2H, m), 1.5 (3H, s), 1.60-1.70 (2H, m), 2.01 (1H, m), 2.83-2.94 (2H, m), 3.39 (2H, m), 3.83 (3H, s), 3.92 (2H, dd, J=11.88 & 4.92 Hz), 7.15 (2H, d, J=8.37 Hz), 7.39 (2H, d, J=8.4 Hz).					
23.			(CH ₂) ₃	386	40
24.			(CH ₂) ₂	336	21
25.			(CH ₂) ₃	310	19
26.				324	47
27.			(CH ₂) ₃	338	47
28.			(CH ₂) ₃	400	61

29.			(CH ₂) ₃	294	11
30.			(CH ₂) ₃	312	33
31.			(CH ₂) ₃	344	20
32.			(CH ₂) ₃	384	24

Preparación 5

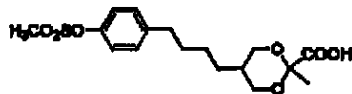
Ácido 2-Metil-5-(5-fenil-5-piridin-4-il-pentil)-
[1,3]dioxano-2-carboxílico (compuesto No. 37)



A una solución de metanólica (10 mL) de metil-[2-metil-5-(5-fenil-5-piridin-4-il-pentil)-[1,3]dioxano-2-carboxilato (compuesto No. 12) (233 mg), preparada como en la preparación 1 anterior se agrega una solución de hidróxido de sodio (50 mg) en agua (5 mL) y la mezcla de reacción se agita a temperatura ambiente durante 15 horas. Los solventes se evaporan bajo presión reducida y se agrega agua (25 mL) al residuo. La mezcla se acidifica con ácido clorhídrico 1 N y se extrae con acetato de etilo (3 X 20 mL). El extracto orgánico combinado se lava con agua (25 mL), solución salina (25 mL), se seca sobre sulfato de sodio y se evapora bajo presión reducida. El producto de goma pegajoso obtenido se tritura con éter de petróleo para producir 150 mg del producto.

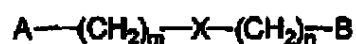
Preparación 6

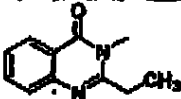
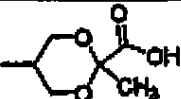
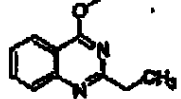
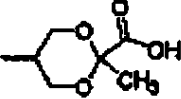
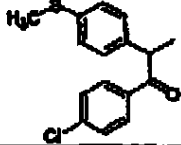
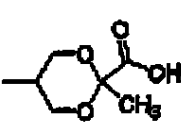
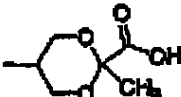
Ácido 5-[4-(4-Metanosulfoniloxi-fenil)-butil]-2-metil-
[1,3]dioxano-2-carboxílico (compuesto No. 50)

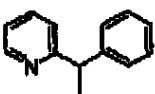
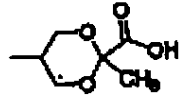
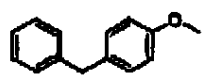
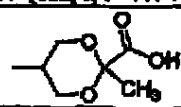
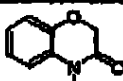
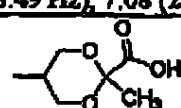
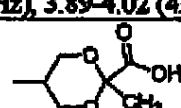
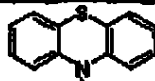
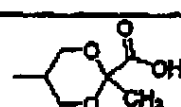
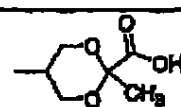
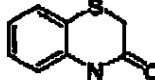
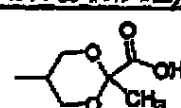


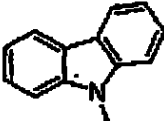
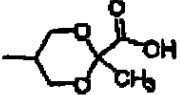
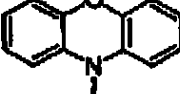
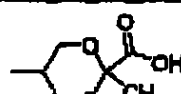
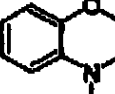
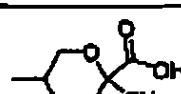
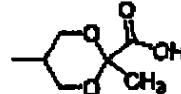
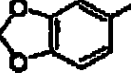
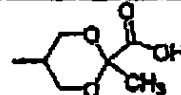
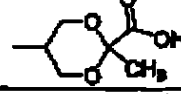
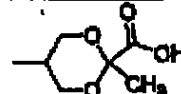
A una solución de Metil-5-[4-(4-metanosulfoniloxi-fenil)-butil]-2-metil-[1,3]dioxano-2-carboxilato (compuesto No. 19) (166 mg) en tetrahidrofurano (2 mL) se agrega otra solución con hidróxido de litio (21 mg) en agua (3 mL) y la mezcla de reacción se agita a temperatura ambiente durante 18 horas. La mezcla de reacción se diluye con agua (20 mL), se acidifica a pH 2-3 con ácido clorhídrico 1N y se extrae con acetato de etilo (3 X 10 mL). El extracto orgánico combinado se lava con agua (20 mL), solución salina (20 mL), se seca sobre sulfato de sodio y se evapora bajo presión reducida para obtener 127 mg del producto.

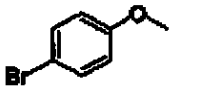
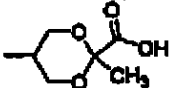
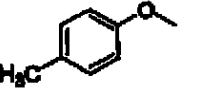
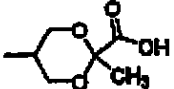
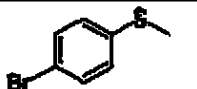
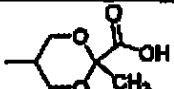
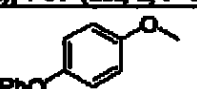
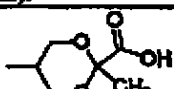
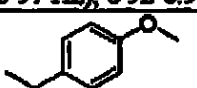
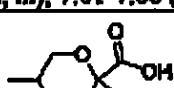
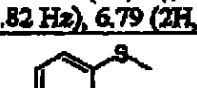
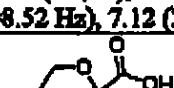
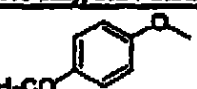
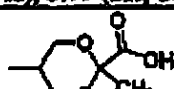
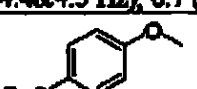
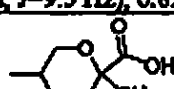
Tabla 2



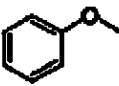
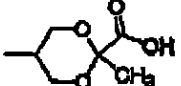
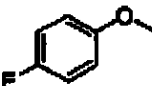
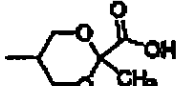
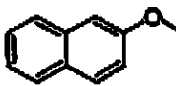
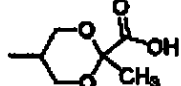
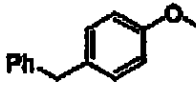
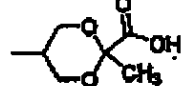
S.No.	A	B	$-(CH_2)_m-X-(CH_2)_n-$	Mol. Wt.	% Yield
33.			$(CH_2)_4$	374	58
	^1H : 1.1 (2H, m), 1.2 (2H, m), 1.4 (3H, t, $J=7.4$ Hz), 1.52 (3H, s), 1.7 (2H, m), 2.0 (1H, m), 2.8 (2H, q, $J=7.4$ Hz), 3.5 (2H, t, $J=11.5$ Hz), 3.9 (2H, dd, $J=11.8$ & 4.5 Hz), 4.0 (2H, t, $J=7.9$ Hz), 7.4 (1H, t, $J=7.3$ Hz), 7.6 (1H, d, $J=8.1$ Hz), 7.7 (1H, t, $J=7.2$ Hz), 8.2 (1H, d, $J=7.5$ Hz).				
34.			$(CH_2)_4$	374	66
	^1H : 1.1 (2H, m), 1.2 (2H, m), 1.4 (3H, t, $J=7.5$ Hz), 1.5 (3H, s), 1.8 (2H, m), 2.0 (1H, s), 3.0 (2H, q, $J=7.5$ Hz), 3.5 (2H, t, $J=11.5$ Hz), 3.9 (2H, dd, $J=11.7$ & 4.3 Hz), 4.6 (2H, t, $J=6.3$ Hz), 7.5 (1H, t, $J=7.3$ Hz), 7.8 (1H, t, $J=7.1$ Hz), 7.9 (1H, d, $J=8.4$ Hz), 8.1 (1H, d, $J=8.2$ Hz).				
35.			$(CH_2)_4$	476.5	97
	^1H : 1.0 (2H, m), 1.2 (2H, m), 1.55 (3H, s), 1.7 (2H, m), 1.9-2.1 (3H, m), 2.4 (3H, s), 3.4 (2H, t, $J=11.8$ Hz), 3.9 (2H, dd, $J=11.7$ & 4.4 Hz), 4.3 (1H, t, $J=7.15$ Hz), 7.16 (4H, m), 7.3 (2H, d, $J=8.46$ Hz), 7.8 (2H, d, $J=8.48$ Hz).				
36.			$(CH_2)_4$	317	59
	^1H : 0.99-1.07 (2H, m), 1.21-1.32 (2H, m), 1.55 (3H, s), 1.76-1.85 (2H, m), 1.98 (1H, m), 3.41 (2H, t, $J=11.59$ Hz), 3.92 (2H, dd, $J=12.0$ & 4.5 Hz), 4.10 (2H, t, $J=6.90$ Hz), 6.48 (1H, d, $J=3.03$ Hz), 7.05 (1H, t, $J=3.0$ Hz), 7.10 (1H, d, $J=7.12$ Hz), 7.19 (1H, t, $J=7.05$ Hz), 7.30 (1H, d, $J=8.19$ Hz), 7.62 (1H, d, $J=7.83$ Hz).				

37.			(CH ₂) ₄	369	55
	¹ H: 0.96 (2H, d, J=6.72 Hz), 1.27 (2H, d, J=6.66 Hz), 1.59 (3H, s), 2.10 (5H, m), 3.43-3.52 (2H, m), 3.93 (2H, q, J=11.55 & 4.26 Hz), 4.28 (1H, t, J=7.65 Hz), 7.14-7.23 (3H, m), 7.31 (4H, m), 7.65 (1H, t, J=7.74 Hz), 8.63 (1H, d, J=4.74 Hz).				
38.			(CH ₂) ₄	384	40
	¹ H: 1.10-1.15 (2H, m), 1.38-1.48 (2H, m), 1.57 (3H, s), 1.63-1.78 (2H, m), 2.05 (1H, m), 3.46 (2H, t, J=11.15 Hz), 3.88-3.94 (4H, m), 3.97-4.02 (2H, dd, J=11.97 & 4.5 Hz), 6.77-6.80 (2H, d, J=8.49 Hz), 7.08 (2H, d, J=8.37 Hz), 7.15-7.29 (5H, m).				
39.			(CH ₂) ₄	349	48
	¹ H: 1.07-1.15 (2H, m), 1.29-1.34 (2H, m), 1.57 (3H, s), 1.59-1.69 (2H, m), 2.03 (1H, m), 3.47 (2H, t, J=11.49 Hz), 3.89-4.02 (4H, m), 4.59 (2H, s), 6.93-7.05 (4H, m).				
40.			(CH ₂) ₄	393	24
	¹ H: 1.12 (2H, m), 1.28 (2H, m), 1.55 (3H, s), 1.64 (2H, dd, J=7.27 & 14.57 Hz), 2.03 (1H, m), 2.20 (2H, m), 3.48 (2H, m), 3.91 (6H, m), 4.67 (1H, t, J=6.44 Hz), 6.99 (4H, m).				
41.			(CH ₂) ₄	399	66
	¹ H: 1.0 (2H, m), 1.36 (2H, m), 1.5 (3H, s), 1.76 (2H, m), 2.0 (1H, m), 3.4 (2H, t, J=11.5 Hz), 3.9 (2H, m), 3.96 (2H, dd, J=4.5 & 11.9 Hz), 6.84 (2H, m), 6.91 (2H, m), 7.15 (4H, d, J=7.0 Hz).				
42.			(CH ₂) ₄	351	84
	¹ H: 1.1 (2H, m), 1.3 (2H, m), 1.57 (3H, s), 1.6 (2H, m), 2.05 (1H, m), 3.0 (2H, dd, J=3.0 & 5.2 Hz), 3.25 (2H, t, J=7.5 Hz), 3.47 (2H, t, J=11.5 Hz), 3.6 (2H, dd, J=5.1 & 7.0 Hz), 4.0 (2H, dd, J=4.44 & 11.9 Hz), 6.6 (2H, m), 7.0 (2H, m).				
43.			(CH ₂) ₄	365	93
	¹ H: 1.1 (2H, m), 1.3 (2H, m), 1.56 (3H, s), 1.6 (2H, m), 2.0 (1H, m), 2.4 (1H, bs), 3.37 (2H, s), 3.48 (2H, t, J=11.5 Hz), 4.0 (4H, m), 7.0 (2H, m), 7.2 (1H, m), 7.38 (1H, d, J=7.5 Hz).				

44.			$(CH_2)_4$	367	74
	¹ H: 1.04 (3H, m), 1.3 (2H, m), 1.53 (3H, s), 1.84 (2H, m), 1.95 (1H, m), 3.4 (2H, t, J=11.5 Hz), 3.9 (2H, dd, J=4.4 & 11.8 Hz), 4.3 (2H, t, J=7.0 Hz), 7.2 (2H, t, J=7.3 Hz), 7.34 (2H, d, J=8.1 Hz), 7.45 (2H, m), 8.1 (2H, d, J=7.71 Hz).				
45.			$(CH_2)_4$	383	70
	¹ H: 1.11 (2H, m), 1.4 (2H, m), 1.57 (3H, s), 1.6 (2H, m), 2.0 (1H, m), 3.5 (4H, t, J=11.5 Hz), 4.0 (2H, dd, J=4.4 & 11.8 Hz), 6.4 (2H, d, J=7.84 Hz), 6.6 (4H, m), 6.77 (2H, m).				
46.			$(CH_2)_4$	335	56
	¹ H: 1.08 (2H, m), 1.3 (2H, m), 1.52-1.62 (5H, m), 2.04 (1H, m), 3.2 (2H, t, J=7.4 Hz), 3.3 (2H, t, J=4.3 Hz), 4.7 (2H, t, J=11.6 Hz), 4.0 (2H, dd, J=4.4 & 11.8 Hz), 4.22 (2H, t, J=4.3 Hz), 6.6 (2H, d, J=7.5 Hz), 6.8 (2H, m).				
47.			$(CH_2)_4$	386	90
	¹ H: 1.1 (2H, m), 1.4 (2H, m), 1.5 (3H, s), 1.7 (2H, m), 2.0 (1H, m), 3.44-3.52 (2H, m), 3.9 (2H, t, J=6.09 Hz), 4.04 (2H, dd, J=4.41 & 11.85 Hz), 6.83 (2H, d, J=8.97 Hz), 6.92-6.97 (4H, m), 7.01-7.06 (1H, m), 7.30 (2H, d, J=7.95 Hz).				
48.			$(CH_2)_3$	308	85
	¹ H: 1.07 (2H, q, J=7.5 Hz), 1.48-1.54 (2H, m), 1.57 (3H, s), 2.01-2.08 (1H, m), 2.50 (2H, t, J=7.47 Hz), 3.45 (2H, t, J=11.58 Hz), 3.95-4.0 (2H, dd, J=4.46 & 11.95 Hz), 5.92 (2H, s), 6.59 (2H, t, J=8.92 Hz), 6.72 (1H, d, J=7.86 Hz).				
49.			$(CH_2)_4$	384	84
	¹ H: 1.04-1.09 (2H, m), 1.23-1.33 (4H, m), 1.53 (3H, s), 1.97-2.05 (1H, m), 2.52 (2H, t, J=7.57 Hz), 3.43 (2H, t, J=11.52 Hz), 3.94-3.99 (2H, dd, J=4.49 & 11.8 Hz), 5.03 (2H, s), 6.8 (2H, d, J=8.4 Hz), 7.05 (2H, d, J=8.43 Hz), 7.29-7.44 (5H, m).				
50.			$(CH_2)_4$	372	80
	¹ H: 1.03-1.10 (2H, q, J=7.51 Hz), 1.28-1.34 (2H, m), 1.53 (3H, s), 1.6 (2H, m), 1.98-2.04 (1H, m), 2.59 (2H, t, J=7.56 Hz), 3.13 (3H, s), 3.44 (2H, t, J=11.65 Hz), 3.93-3.99 (2H, dd, J=4.68 & 11.94 Hz), 7.18 (4H, s).				

51.			(CH ₂) ₃	359	45
	¹ H: 1.20-1.28 (2H, m), 1.58 (3H, s), 1.70-1.79 (2H, m), 2.05-2.13 (1H, m), 3.8 (2H, t, J=6.075 Hz), 4.0-4.05 (2H, m), 6.73 (2H, d, J=8.82 Hz), 7.35 (2H, d, J=8.85 Hz).				
52.			(CH ₂) ₃	294	74
	¹ H: 1.20-1.28 (2H, m), 1.58 (3H, s), 1.71-1.76 (2H, m), 2.1 (1H, m), 2.27 (3H, s), 3.46-3.54 (2H, m), 3.89 (2H, t, J=6.13 Hz), 4.03 (2H, dd, J=11.88 & 4.47 Hz), 6.76 (2H, d, J=8.43 Hz), 7.06 (2H, d, J=8.34 Hz).				
53.			(CH ₂) ₃	375	10
	¹ H: 1.15-1.18 (2H, m), 1.5 (3H, s), 1.59-1.6 (2H, m), 1.99-2.06 (1H, m), 2.85 (2H, t, J=7.06 Hz), 3.42-3.49 (2H, m), 3.95 (2H, dd, J=11.88 & 4.34 Hz), 7.16 (2H, d, J=8.4 Hz), 7.39 (2H, d, J=8.43 Hz).				
54.			(CH ₂) ₃	372	37
	¹ H: 1.22-1.29 (2H, m), 1.72 (3H, s), 1.73-1.78 (2H, m), 2.04-2.14 (1H, m), 3.47-3.55 (2H, m), 3.9 (2H, t, J=6.09 Hz), 4.04 (2H, dd, J=4.41 & 11.85 Hz), 6.83 (2H, d, J=8.97 Hz), 6.92-6.97 (4H, m), 7.01-7.06 (1H, m), 7.30 (2H, d, J=7.95 Hz).				
55.			(CH ₂) ₃	322	67
	¹ H: 1.22 (6H, s), 1.25-1.28 (2H, m), 1.58 (3H, s), 1.69-1.78 (2H, m), 2.1 (1H, m), 2.80-2.89 (1H, m), 3.46-3.54 (2H, m), 3.90 (2H, t, J=6.1 Hz), 4.02 (2H, dd, J=4.62 & 11.82 Hz), 6.79 (2H, d, J=8.52 Hz), 7.12 (2H, d, J=8.52 Hz).				
56.			(CH ₂) ₃	296	77
	¹ H: 1.12-1.04 (2H, m), 1.31 (3H, s), 1.44-1.54 (2H, m), 1.83-1.84 (1H, m), 2.90 (2H, t, J=7.1 Hz), 3.24-3.32 (2H, m), 3.79 (2H, dd, J=4.2 & 11.46 Hz), 7.13-7.29 (5H, m).				
57.			(CH ₂) ₃	310	82
	¹ H: 1.20-1.28 (2H, q, J=7.6 Hz), 1.58 (3H, s), 1.68-1.77 (2H, m), 2.07-2.13 (1H, m), 3.5 (2H, t, J=11.5 Hz), 3.76 (3H, s), 3.87 (2H, t, J=6.1 Hz), 4.0-4.06 (2H, dd, J=4.4 & 4.5 Hz), 6.7 (2H, d, J=9.5 Hz), 6.83 (2H, d, J=4.57 Hz).				
58.			(CH ₂) ₃	386	71
	¹ H: 1.20-1.28 (2H, q, J=7.5 Hz), 1.58 (3H, s), 1.70-1.82 (2H, m), 2.05-2.11 (1H, m), 3.5 (1H, t, J=11.5 Hz), 3.82-4.0 (5H, m), 5.0 (2H, s), 6.77-6.91 (4H, m), 7.25 (1H, s), 7.28-7.42 (4H, m).				

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59.			(CH ₂) ₃	280	55
¹ H: 1.07-1.14 (2H, q, J=7.5 Hz), 1.32 (3H, s), 1.60-1.69 (2H, m), 1.84-1.92 (1H, m), 3.32-3.36 (2H, m), 3.84-3.95 (4H, m), 6.89 (3H, t, J=6.51 Hz), 7.25 (2H, t, J=7.89 Hz).					
60.			(CH ₂) ₃	298	82
¹ H: 1.21-1.29 (2H, m), 1.59 (3H, s), 1.70-1.79 (2H, m), 2.0-2.14 (1H, m), 3.47-23.5 (2H, m), 3.86-3.92 (2H, m), 4.10-4.06 (2H, dd, J=4.5 & 11.7 Hz), 6.77-6.82 (2H, m), 6.97 (2H, d, J=8.7 Hz).					
61.			(CH ₂) ₃	330	83
¹ H: 1.26-1.34 (2H, q, J=7.76 Hz), 1.59 (3H, s), 1.76-1.90 (2H, m), 2.10-2.17 (1H, m), 3.49-3.57 (2H, m), 4.0-4.12 (4H, m), 7.1 (2H, d, J=9 Hz), 7.32 (1H, t, J=7.23 Hz), 7.43 (1H, t, J=7.25 Hz), 7.69-7.7 (3H, m).					
62.			(CH ₂) ₃	370	80
¹ H: 1.20-1.27 (2H, q, J=7.6 Hz), 1.58 (3H, s), 1.58-1.71 (2H, m), 2.0-2.11 (1H, m), 3.46-3.54 (2H, m), 3.87-3.96 (4H, m), 3.99-4.0 (2H, dd, J=4.65 & 11.8 Hz), 6.8 (2H, d, J=7.72 Hz), 7.0 (2H, d, J=8.43 Hz), 7.17 (3H, d, J=7.73 Hz), 7.24-7.29 (2H, m).					

Preparación de sales

Sales de sodio y potasio de los compuestos en la tabla 2 se preparan al seguir el procedimiento general descrito adelante.

A una solución de derivados de ácido carboxílico de los compuestos novedosos (mencionados en la tabla 2) (1 mmol) en solvente alcohólico como metanol, etanol, y similares se agrega otra solución de alcóxido de sodio o potasio (0.95 mmol) en un solvente alcohólico y la mezcla de reacción se agita durante 3 horas a 25-30° C. el solvente se evapora y el residuo se tritura con éter de dietilo o éter diisopropilo seco para obtener la sal del ácido carboxílico correspondiente.

Los compuestos de la presente invención reducen los triglicéridos, colesterol total, LDL, VLDL, e incrementan el HDL y reducen los niveles de glucosa en suero. Esto de demuestra mediante experimentos animales in vivo.

A) demostración de la eficacia *in vivo* de compuestos:

i) Actividad de reducción de colesterol total y triglicérido en suero en ratones albinos suizos

Se incuban ratones albinos suizos machos (SAM) en jaulas para animales Zydus. Todos estos animales se mantienen bajo ciclo de 12 horas de luz y oscuridad a $25 \pm 1^\circ$ C. A los animales se les da concentrado de laboratorio estándar (NIN, Hyderabad, India) y agua ad libitum. Se utiliza SM de 20-30 g de peso corporal. Se utiliza el protocolo aprobado por el Institutional Animal Ethics Committee.

Los compuestos de ensayo se administran oralmente a ratones albinos Suizos a 0.001 a 50 mg/kg/día de dosis durante 6 días. El compuesto se administra después de suspenderlo en 0.25% CMC o disolverlo en agua, cuando el compuesto es soluble en agua. Los ratones de control se tratan con vehículo (0.25 % de Carboximetilcelulosa; dosis 10 ml/kg).

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Las muestras de sangre se recolectan en el día 0 y en estado alimentado 1 hora después de administración de la droga en el día 6 del tratamiento. Se recolecta la sangre en capilares heparinizados y el suero se analiza para colesterol total y triglicéridos (Wieland, O Methods of Enzymatic analysis. Bergermeyer, H., O., Ed., 1963.211-214; Trinder, P. Ann. Clin. Biochem. 1969.6: 24-27). Medición del colesterol total y trigliceridos se utilizando kits comerciales (Zydus-Cadila, Pathline, Ahmedabad, India).

Fórmula de cálculo

El porcentaje de reducción en colesterol total/triglicéridos se calcula con la fórmula:

Porcentaje de reducción (%) =

$$1 - \left[\frac{TT/OT}{TC/OC} \right] \times 100$$

OC= Valor del grupo de control en el día cero OT= Valor
del grupo tratado en el día cero

TC= Grupo de control día de ensayo TT= Grupo tratado día de
ensayo

Tabla 1:

Actividad de reducción de triglicéridos en ratones albinos
Suizos:

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Ejemplo No.	Dosis (mg/kg/día)	% de reducción de Triglicéridos
50	10	32
38	10	32
49	10	26

ii) Actividad de reducción de colesterol total y triglicéridos en suero en Hámster de mancha dorada Siria

Hámster de machos y hembras de mancha dorada Sirias se incuban en jaulas para animales Zydus. Todos estos animales se mantienen bajo ciclo de de luz y oscuridad de 12 horas a 22±3 grados C. Se utiliza el protocolo aprobado por el Institutional Animal Ethics Committee. Dos grupos de animales se colocan en dieta HF-HC (alta grasa y alto colesterol) durante 14 días. En el día 14 todas las dietas fueron HF-HC mientras que un grupo de animales se coloca en dieta normal durante dos semanas.

Un grupo de animales en dieta HF-HC se trata (po) con compuestos de la presente invención, a 0.001 a 50 me/kg diario durante 15 días mediante el otro grupo recibe el vehículo. Después de que se recolectan muestras de sangre durante 15 días en capilares heparinizados de animales para la determinación de colesterol total (TC), triglicéridos (TG) (Wieland, O. Mehtods of Enzymatic analysis. Bergermeyer, H.,

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O., Ed., 1963.211-214; Trinder, P. Ann. Clin. Biochem. 1969.6: 24-27). Se hace la medición del triglicérido en suero y colesterol utilizando kits comerciales (Pointe Scientific. Inc. USA.).

Fórmula de cálculo:

Se calcula el porcentaje de reducción total en colesterol total/ triglicéridos de acuerdo con la fórmula:

Porcentaje de reducción (%)= (TT-TC)/TC*100

TC= Grupo de control día ensayo TT= Grupo tratado día ensayo.

Tabla 2:

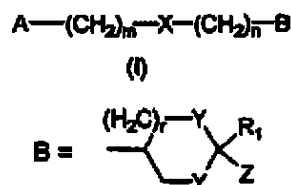
Ejemplo No.	Dosis (mg/kg/día)	% de reducción de Triglicéridos
50	3	45

No se observan efectos adversos para ninguno de los compuestos mencionados de la invención. Los compuestos de la presente invención muestran buena actividad de reducción de colesterol y lípidos, y glucosa de suero en los animales utilizados como experimento. Estos compuestos son útiles para el ensayo/profilaxis de enfermedades originadas por hiperlipidemia, hipercolesterolemia, hiperinsulinemia, hiperglicemia tales como NIDDM, enfermedades cardiovasculares apoplejía, hipertensión, obesidad debido a tales enfermedades se interrelaciona la una con la otra.

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REIVINDICACIONES

1. Un compuesto de fórmula (I):



sus forma tautoméricas, sus sales farmacéuticamente aceptables, sus solvatos farmacéuticamente aceptables, las composiciones farmacéuticas que las contienen, en donde 'A' representa un grupo arilo, cicloalquilo simple o fusionado opcionalmente sustituido, o un grupo heteroarilo opcionalmente sustituido o heterociclilo opcionalmente sustituido; 'm' = 0-2 ; 'n' = 3-6; 'X' representa O, S, -N-(Ra)- o -CH₂-; Ra representa H, un grupo alquilo, acilo o arilo, aralquilo sustituido o no sustituido, lineal o ramificado; 'Y' en cada ocurrencia independientemente representa O o S; R₁ representa H, alquilo sustituido o no sustituido lineal o ramificado; r = 0-2; Z representa -(CH₂)_sCOOH, alcóxicarbonilo, hidroximetilo, -CN, tetrazoles sustituido o no sustituido, grupos alquilcarbonilo, s = 0-4; con la condición de que cuando 'X' = CH₂ y

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- i) 'A' representa un grupo heterocíclico sustituido, las sustituciones sobre 'A' no representan un grupo arilo, aromático, heterocíclico o cicloalquilo; y
- ii) 'A' representa un grupo arilo sustituido, el sustituyente sobre 'A' representa un grupo alquilsulfonilo, arilo, ariloxi, aralcoxi, cicloalquilo, heteroarilo o heterocíclico.

2. Un compuesto como se reivindica en la reivindicación 1 en donde, cuando 'A' es sustituido, las sustituciones adecuadas sobre 'A' se pueden seleccionar de hidroxilo, oxo, halo, tio, nitro, amino, ciano, formilo, o grupos sustituidos o no sustituidos seleccionados de amidino, alquilo, haloalquilo, perhaloalquilo, alcoxi, haloalcoxi, perhaloalcoxi, alqueno, alquino, cicloalquilo, cicloalqueno, bicicloalquilo, bicicloalqueno, alcoxi, alqueno, cicloalcoxi, arilo, ariloxi, aralquilo, aralcoxi, acilo, aciloxi, acilamino, amino monosustituido o disustituido, arilamino, aralquilamino, ácido carboxílico y sus derivados tales como ésteres y amidas, carbonilamino, hidroxialquilo, aminoalquilo, alcoxialquilo, ariloxialquilo, aralcoxialquilo, alquiltio, tioalquilo, ariltio, alquilsulfonilamino, alquilsulfonilo, alcóxicarbonilamino, ariloxicarbonilamino, aralquiloalcoxicarbonilamino,

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aminocarbonilamino, alquilaminocarbonilamino,
alcoxi-amino, hidroxilamino, derivados de sulfenilo,
derivados de sulfonilo.

3. Un compuesto como se reivindica en la reivindicación 1 en donde, Las sustituciones adecuadas sobre 'B' se pueden seleccionar de hidroxilo, oxo, halo, tio, nitro, amino, ciano, formilo, o grupos sustituidos o no sustituidos seleccionados de alquilo, haloalquilo, o grupos arilo.

~~4.~~ Un compuesto como se reivindica en la reivindicación 1 en donde, las sustituciones adecuadas de cualquiera de los sustituyentes 'A' & 'B' se pueden seleccionar de hidroxilo, oxo, halo, tio, nitro, amino, ciano, formilo, o grupos sustituidos o no sustituidos seleccionados de amidino, alquilo, haloalquilo, perhaloalquilo, alcoxi, haloalcoxi, perhaloalcoxi, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, bicicloalquilo, bicicloalquenilo, alcoxi, alquenoxi, cicloalcoxi, arilo, ariloxi, aralquilo, aralcoxi, acilo, aciloxi, acilamino, amino monosustituido o disustituido, arilamino, aralquilamino, ácido carboxílico y sus derivados tales como ésteres y amidas, carbonilamino, hidroxialquilo, aminoalquilo, alcoxialquilo, ariloxialquilo, aralcoxialquilo, alquiltio, tioalquilo, ariltio, alquilsulfonilamino,

alquilsulfoniloxi, alcoxycarbonilamino,
ariloxycarbonilamino, aralquiloxy-carbonilamino,
aminocarbonilamino, alquilaminocarbonilamino,
alcoxi-amino, hidroxilamino, derivados de sulfenilo, y
derivados de sulfonilo.

 Los compuestos de la reivindicación 1-3 se seleccionan
de

Metil-5-[4-(2-etil-4-oxo-4H-quinazolin-3-il)-butil]-2-
metil-[1,3]dioxano-2-carboxilato;

Metil-5-[4-(2-etil-quinazolin-4-iloxi)-butil]-2-metil-
[1,3]dioxano-2-carboxilato;

Metil-5-[6-(4-cloro-fenil)-5-(4-metilsulfanil-fenil)-6-
oxo-hexil]-2-metil-[1,3]dioxano-2-carboxilato;

Metil-5-[4-(2,3-dihidro-benzo[1,4]oxazin-4-il)-butil]-2-
metil-[1,3]dioxano-2-carboxilato;

Metil-2-metil-5-(4-fenoxazin-10-il-butyl)-[1,3]dioxano-
2-carboxilato;

Metil-5-[4-(6,7-dihidro-4H-tieno[3,2-c]piridin-5-il)-
butil]-2-metil-[1,3]dioxano-2-carboxilato;

Metil-5-(4-carbazol-9-il-butyl)-2-metil-[1,3]dioxano-2-
carboxilato;

Metil-2-metil-5-[4-(3-oxo-2,3-dihidro-benzo[1,4]tiazin-
4-il)-butil]-[1,3]dioxano-2-carboxilato;

Metil-5-[4-(2,3-dihidro-benzo[1,4]tiazin-4-il)-butil]-2-
metil-[1,3]dioxano-2-carboxilato;

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Metil-2-metil-5-(4-fenotiazin-10-il-butil)-[1,3]dioxano-2-carboxilato;

Metil-5-(4-indol-1-il-butil)-2-metil-[1,3]dioxano-2-carboxilato ;

Metil-2-metil-5-(5-fenil-5-piridin-4-il-pentil)-[1,3]dioxano-2-carboxilato;

Metil-5-[4-(4-bencil-fenoxi)-butil]-2-metil-[1,3]dioxano-2-carboxilato ;

Metil-2-metil-5-[4-(3-oxo-2,3-dihidro-benzo[1,4]oxazin-4-il)-butil]-[1,3]dioxano-2-carboxilato;

Metil-5-{4-[2-(2-hidroxi-etil)-3-oxo-2,3-dihidro-benzo[1,4]oxazin-4-il]-butil}-2-metil-[1,3]dioxano-2-carboxilato;

Metil-2-metil-5-[4-(4-fenoxi-fenoxi)-butil]-[1,3]dioxano-2-carboxilato;

Metil-5-(3-benzo[1,3]dioxol-5-il-propil)-2-metil-[1,3]dioxano-2-carboxilato ;

Metil-5-[4-(4-metanosulfoniloxi-fenil)-butil]-2-metil-[1,3]dioxano-2-carboxilato;

Metil-5-[4-(4-benciloxi-fenil)-butil]-2-metil-[1,3]dioxano-2-carboxilato ;

Metil-2-metil-5-(3-fenilsulfanil-propil)-[1,3]dioxano-2-carboxilato;

Etil-5-[3-(4-bromo-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxilato;

Metil-2-metil-5-[3-(4-fenoxi-fenoxi)-propil]-[1,3]dioxano-2-carboxilato;

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Metil-5-[3-(4-isopropil-fenoxi)-propil]-2-metil-
[1,3]dioxano-2-carboxilato ;

Metil-2-metil-5-(3-p-toliloxi-propil)-[1,3]dioxano-2-
carboxilato;

Metil-5-[3-(4-bromo-fenilsulfanil)-propil]-2-metil-
[1,3]dioxano-2-carboxilato;

Metil-2-metil-5-(3-fenoxi-propil)-[1,3]dioxano-2-
carboxilato;

Metil-5-[3-(4-fluoro-fenoxi)-propil]-2-metil-
[1,3]dioxano-2-carboxilato;

Metil-2-metil-5-[3-(naftalen-2-iloxi)-propil]-
[1,3]dioxano-2-carboxilato;

Metil-5-[3-(4-benciloxi-fenoxi)-propil]-2-metil-
[1,3]dioxano-2-carboxilato;

Metil-5-[3-(4-metoxi-fenoxi)-propil]-2-metil-
[1,3]dioxano-2-carboxilato;

Metil-5-[3-(4-bencil-fenoxi)-propil]-2-metil-
[1,3]dioxano-2-carboxilato;

Ácido 5-[4-(2-Etil-4-oxo-4H-quinazolin-3-il)-butil]-2-
metil-[1,3]dioxano-2-carboxílico y sus sales
farmacéuticamente aceptables;

Ácido 5-[4-(2-Etil-quinazolin-4-iloxi)-butil]-2-metil-
[1,3]dioxano-2-carboxílico y sus sales
farmacéuticamente aceptables;

Ácido 5-[6-(4-Cloro-fenil)-5-(4-metilsulfanil-fenil)-6-
oxo-hexil]-2-metil-[1,3]dioxano-2-carboxílico y sus
sales farmacéuticamente aceptables;

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Ácido 5-[4-(2,3-Dihidro-benzo[1,4]oxazin-4-il)-butil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-(4-fenoxazin-10-il-butyl)-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-(4-Carbazol-9-il-butyl)-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-[4-(3-oxo-2,3-dihidro-benzo[1,4]tiazin-4-il)-butil]-[1,3]dioxano-2-ácido carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[4-(2,3-Dihidro-benzo[1,4]tiazin-4-il)-butil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-(4-fenotiazin-10-il-butyl)-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-(4-Indol-1-il-butyl)-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-(5-fenil-5-piridin-4-il-pentil)-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[4-(4-Bencil-fenoxi)-butyl]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-[4-(3-oxo-2,3-dihidro-benzo[1,4]oxazin-4-il)-butil]-[1,3]dioxano-2-ácido carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-{4-[2-(2-Hidroxi-etil)-3-oxo-2,3-dihidro-benzo[1,4]oxazin-4-il]-butil}-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-[4-(4-fenoxi-fenoxi)-butil]-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-(3-Benzo[1,3]dioxol-5-il-propil)-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[4-(4-Metanosulfonilo-xi-fenil)-butil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[4-(4-Benciloxi-fenil)-butil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-(3-fenilsulfanil-propil)-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[3-(4-Bromo-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-[3-(4-fenoxi-fenoxi)-propil]-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

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Ácido 5-[3-(4-Isopropil-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-(3-p-toliloxi-propil)-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[3-(4-Bromo-fenilsulfanil)-propil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-(3-fenoxi-propil)-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[3-(4-Fluoro-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 2-Metil-5-[3-(naftalen-2-iloxi)-propil]-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[3-(4-Benciloxi-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[3-(4-Metoxi-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

Ácido 5-[3-(4-Bencil-fenoxi)-propil]-2-metil-[1,3]dioxano-2-carboxílico y sus sales farmacéuticamente aceptables;

6. Una composición farmacéutica que comprende compuestos de fórmula (I), como se reivindica en las reivindicaciones precedentes y un vehículo farmacéuticamente aceptable, diluyente, excipiente o solvato.
7. Un método para prevenir o tratar enfermedades causadas por hiperlipidemia, hipercolesterolemia, hiperglicemia, obesidad, tolerancia dañina a la glucosa, resistencia a la leptina, resistencia a la insulina, complicaciones diabéticas, comprende administrar una cantidad no tóxica efectiva, del compuesto de fórmula (I) o composiciones farmacéuticas adecuadas como se define en cualquiera de las reivindicaciones precedentes a un paciente en necesidad de este.
8. El método de acuerdo con cualquiera de la reivindicaciones precedentes, en donde la enfermedad es diabetes tipo 2, tolerancia dañina a la glucosa, dislipidemia, hipertensión, obesidad, aterosclerosis, hiperlipidemia, enfermedad cardíaca coronaria, enfermedades cardiovasculares, y otras enfermedades en donde la resistencia a la insulina es el mecanismo patofisiológico subyacente.

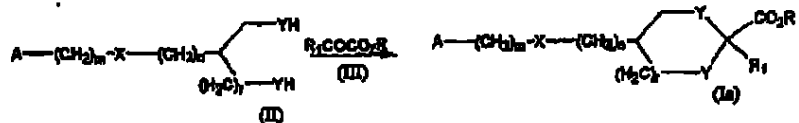
2/11

9. Una medicina para tratar/reducir cualquiera de las condiciones de enfermedad descritas en cualquiera de las reivindicaciones precedentes que comprende administrar un compuesto de fórmula (I), como se define en las reivindicaciones 1-5, y un vehículo farmacéuticamente aceptable, diluyente, excipientes, o solventes a un paciente en necesidad de esta.

10. El uso de compuestos fórmula (I), sus composiciones farmacéuticas, y medicinas contenidas como se define en las reivindicaciones previas como un medicamento adecuado para el tratamiento de las enfermedades mencionadas en cualquiera de las reivindicaciones mencionadas anteriormente.

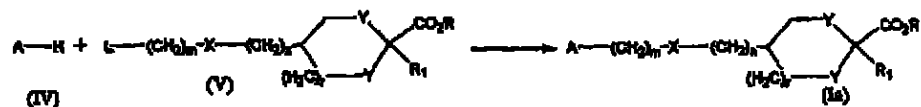
11. Un proceso para la preparación del compuesto de fórmula (I) comprende las etapas de

i) Hacer reaccionar un compuesto de fórmula (II) con un compuesto de fórmula (III) en donde R representa grupo alquilo adecuado y todos los otros símbolos son como se define en la reivindicación 1, para obtener un compuesto de fórmula (Ia)



ii) alternativamente, hacer reaccionar un compuesto de fórmula (IV) con un compuesto de fórmula (V), en

donde 'L' representa un grupo saliente adecuado y 'R' representa un grupo alquilo adecuado y todos los otros símbolos son como se define en la reivindicación 1, para obtener un compuesto de fórmula (Ia), en donde todos los símbolos son como se define en la reivindicación 1.



iii) convertir el compuesto de fórmula (Ia) a un compuesto de fórmula (I), en donde todos los símbolos son como se define en la reivindicación 1.



From the INTERNATIONAL BUREAU

PCTNOTIFICATION CONCERNING
TRANSMITTAL OF COPY OF INTERNATIONAL
APPLICATION AS PUBLISHED OR REPUBLISHED

To.

SUBRAMANIAM, Hanharan
Subramaniam, Nataraj & Associates
E-556, Greater Kailash II
New Delhi - 110 048
INDEReceived with
ThanksDate of mailing (day/month/year)
25 August 2005 (25.08.2005)Applicant's or agent's file reference
ZRC-MC-021

24 AUG 2005

IMPORTANT NOTICE

SN&A

International application No.
PCT/IN2005/000011International filing date (day/month/year)
07 January 2005 (07.01.2005)Priority date (day/month/year)
09 January 2004 (09.01.2004)

Applicant

CADILA HEALTHCARE LIMITED et al

The International Bureau transmits herewith the following documents:

copy of the international application as published by the International Bureau on 25 August 2005 (25.08.2005) under
No. WO 2005/077943copy of international application as republished by the International Bureau on under
No. WOFor an explanation as to the reason for this republication of the international application, reference is made to INID codes (15), (48)
or (88) (as the case may be) on the front page of the attached document.The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Dorothee Mülhausen

Facsimile No. +41 22 740 14 35

Facsimile No. +41 22 338 87 40

Form PCT/IB/311 (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN2005/000011

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D405/06 C07D319/06 C07D413/06 C07D495/04 C07D417/06
C07D407/06 A61K31/357 A61P3/04 C07D405/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 295 875 A (NIPPON SHINYAKU CO., LTD) 26 March 2003 (2003-03-26) cited in the application page 7, line 10 - line 42; claims 1,10	1-4,6-11
X	ASAKI, T. ET AL.: "A novel 1,3-dioxane-2-carboxylic acid derivative, NS-220, as a highly potent and selective PPARalpha agonist." ALBANY MOLECULAR RESEARCH, INC. TECHNICAL REPORTS, vol. 7, no. 46, 2002, pages 8-9, XP002332373 the whole document	1-4,6-10



Further documents are listed in the continuation of box C



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *S* document member of the same patent family

Date of the actual completion of the international search

17 June 2005

Date of making of the international search report

30/06/2005

Name and mailing address of the ISA

European Patent Office, P.B. 6818 Patentplan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Johnson, C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN2005/000011

119

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	WO 00/04011 A (MERCK PATENT GMBH; BERTHELOM, JEAN-JACQUES; GUERRIER, DANIEL; RASPE, E) 27 January 2000 (2000-01-27) cited in the application claim 1	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2005/000011

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 7-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IN2005/000011

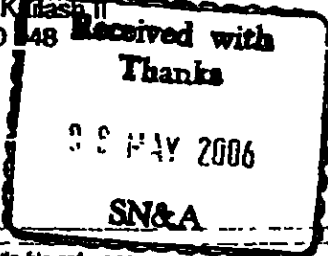
Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1295875	A	26-03-2003	AU 5884101 A	03-12-2001
			BR 0111199 A	01-04-2003
			CA 2410382 A1	25-11-2002
			EP 1295875 A1	26-03-2003
			HU 0302397 A2	28-11-2003
			JP 3591514 B2	24-11-2004
			MX PA02011609 A	27-03-2003
			NO 20025659 A	25-11-2002
			UA 72625 C2	15-04-2003
			US 2005009785 A1	13-01-2005
			CN 1430612 A	16-07-2003
			WO 0190087 A1	29-11-2001
			JP 2004250460 A	09-09-2004
			US 2003166697 A1	04-09-2003
			US 2005009892 A1	13-01-2005
			US 2004162325 A1	19-08-2004
			ZA 200209152 A	11-02-2004
WO 0004011	A	27-01-2000	FR 2781222 A1	21-01-2000
			AT 235485 T	15-04-2003
			AU 753287 B2	17-10-2002
			AU 5034799 A	07-02-2000
			BR 9912138 A	10-04-2001
			CA 2337481 A1	27-01-2000
			CN 1309655 A	22-08-2001
			DE 69906303 D1	30-04-2003
			DE 69906303 T2	11-12-2003
			DK 1098893 T3	07-07-2003
			WO 0004011 A1	27-01-2000
			EP 1098893 A1	16-05-2001
			ES 2192853 T3	16-10-2003
			HU 0103411 A2	29-04-2002
			ID 27854 A	26-04-2001
			JP 2002520407 T	09-07-2002
			NO 20010266 A	16-01-2001
			PL 345397 A1	17-12-2001
			PT 1098893 T	29-08-2003
			SI 1098893 T1	31-10-2003
			SK 482001 A3	11-09-2001
			US 6528538 B1	04-03-2003
			ZA 200101303 A	15-05-2002

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E-556, Greater Kailash II
New Delhi - 110 048
INDE



PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(PCT Rule 71.1)

Date of mailing
(day/month/year) 04.05.2006

Applicant's or agent's file reference
ZRC-MC-021

IMPORTANT NOTIFICATION

International application No. PCT/IN2005/000011	International filing date (day/month/year) 07.01.2005	Priority date (day/month/year) 09.01.2004
--	--	--

Applicant
CADILA HEALTHCARE LIMITED

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4 REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority.



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Krage, D
Tel +49 89 2399-7530



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ZHC-MC-021		FOR FURTHER ACTION	See Form PCT/PEA/416
International application No. PCT/IN2005/000011	International filing date (day/month/year) 07.01.2005	Priority date (day/month/year) 09.01.2004	
International Patent Classification (IPC) or national classification and IPC INV. C07D405/06 C07D319/06 C07D413/06 C07D495/04 C07D417/06 C07D407/06 A61K31/357 A61P3/04 C07D405/12			
Applicant CADILA HEALTHCARE LIMITED			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36 2. This REPORT consists of a total of 7 sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ sent to the applicant and to the International Bureau) a total of 1 sheets, as follows: ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions)			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☐ Box No. VIII Certain observations on the international application			
Date of submission of the demand 29.07.2005		Date of completion of this report 04.05.2006	
Name and mailing address of the international preliminary examining authority  European Patent Office D-80298 Munich Tel +49 89 2399 - 0 Tx 523656 epmu d Fax +49 89 2399 - 4465		Authorized officer Johnson, C Telephone No. +49 89 2399-8287 	

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No
PCT/IN2005/000011

Box No. I Basis of the report

- 1 With regard to the language, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))
2. With regard to the elements* of the international application, this report is based on *(replacement sheets, which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report).*

Description, Pages

1-34 as originally filed

Claims, Numbers

2(part), 3-11 as originally filed

1, 2(part) received on 26.09.2005 with letter of 23.09.2005

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify):*
- ☐ any table(s) related to sequence listing *(specify):*

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☒ the claims, Nos. 1
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify):*
- ☐ any table(s) related to sequence listing *(specify):*

* If item 4 applies, some or all of these sheets may be marked "superseded"

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No
PCT/IN2005/000011

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of.

☐ the entire international application.

☒ claims Nos. 5(part), 7-10

because.

☒ the said international application, or the said claims Nos. 7-10 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 5(part) are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*).

☒ no international search report has been established for the said claims Nos. 5(part)

☐ a meaningful opinion could not be formed without the sequence listing, the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b) and 13ter.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

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**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/IN2005/000011

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	5
	No: Claims	1-4,6-11
Inventive step (IS)	Yes: Claims	5
	No: Claims	1-4 6 11
Industrial applicability (IA)	Yes: Claims	1-6 11
	No: Claims	

2. Citations and explanations (Rule 70.7)

see separate sheet

I. Basis of the report

The amendments filed with the letter dated 23.9.05 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. In the original disclosure proviso i) excluded compounds wherein X is CH₂, A is a substituted heterocyclic group wherein the substituent is aryl, aromatic, heterocyclic or cycloalkyl. However, these compounds are no longer excluded. Therefore the presently amended claim 1 extends to compounds which were not part of the original disclosure. In addition, the amended proviso i) amounts to a newly introduced proviso, as its content is different from that in the original disclosure. The European Patent Office allows disclaimers without basis in the original application to be introduced only to exclude subject matter from a disclosure which is considered to be an "accidental anticipation". A disclosure is considered to be an accidental anticipation if it is so unrelated to and remote from the claimed invention that the person skilled in the art would never have taken it into consideration when making the invention. However, the amended proviso has been introduced to exclude compounds of D1. This document is considered to be highly relevant for the assessment of inventive step as it concerns compounds with the same activity. Thus a disclaimer newly introduced to exclude compounds of D1 is not allowable. As the amendments are not allowable the following examination has been performed for the claims in their original form.

III. Non-establishment of opinion

Claims 7-10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

There are 2 claims numbered "3" and no claim 5. The following examination has been based on the claims wherein the 2nd claim presently numbered "3" is treated as claim 4 and present claim 4 is renumbered as claim 5.

A number of examples (3, 12, 17, 26, 35, 37, 48) do not fall within the scope of formula (I) of present claim 1. These examples are claimed in claim 5 as being compounds of claims 1-3. This introduces a contradiction into the claims, which

creates a lack of clarity (Article 6 PCT) concerning the scope of the claims. Only formula (I) has been searched, thus no opinion will be established for those compounds of claim 5 not falling within this formula.

V. Reasoned statement

Reference is made to the following documents:

D1: EP-A-1 295 875

D2: Albany Molecular Research, Inc Technical Reports, vol. 7. no. 46, 2002, p. 8-9

D3: WO00/04011

Novelty

In claim 1 compounds wherein A is i.a. optionally substituted heteroaryl or optionally substituted heterocyclyl are claimed. Thus it is clear that the term "heterocyclyl" does not include heteroaryl - if it did, both possibilities would not be separately listed in the claim. In proviso i) compounds wherein A is heterocyclyl having aryl, aromatic, heterocyclic or cycloalkyl substituents are excluded. No mention is made of an exclusion of compounds wherein A is heteroaryl having these substituents. D1 discloses a general formula [1] wherein the group corresponding to the present A is a divalent aromatic heterocyclic group, i.e. a heteroaryl group. This disclosure overlaps with the present claims. The compounds are described as being effective at lowering triglyceride, LDL-C and insulin levels in the blood and can thus be useful in the treatment of i.a. diabetes and obesity. Furthermore, D1 discloses specific compounds falling within the scope of the present claims (e.g. the compounds of examples 1-4). D2 elaborates on the mechanism of action of one of the compounds of D1, stating that it is a selective PPAR-alpha activator.

These disclosures are novelty-destroying for present claims 1-4 and 6-11.

D3 discloses general formula I wherein R² or R³ may be (C₆-C₁₀)aryl(C₁-C₇)alkyl wherein the aryl group may optionally be substituted. In present claim 1, proviso ii) excludes certain compounds wherein A is a substituted aryl group, however there is no exclusion of compounds wherein A is an unsubstituted aryl group. The compounds of D3 are described as being activators of PPAR-alpha and gamma, useful as hypolipidemic and hypoglycemic agents. Thus the disclosure of D3 overlaps with present claims 1, 3 and 7-10.

Claims 1-4 and 6-11 do not fulfil the requirements of Article 33(2) PCT.

Inventive step

In view of their lack of novelty, claims 1-4 and 6-11 cannot be inventive.

Re. those compounds of claim 5 which fall within the scope of formula (I).

For those compounds wherein A is heterocyclic or heteroaryl, D1 is taken as the closest prior art. The compounds of D1 all have 2 rings directly attached to one another (R¹-Het-). None of the compounds of claim 5 have this feature. It does not appear obvious to provide further compounds with PPAR modulating activity by replacing the R¹ ring of D1 by one of the substituents given in claim 5. Thus for the compounds wherein A is heterocyclic or heteroaryl, claim 5 may be considered inventive.

For the compounds wherein A is aryl, D3 may be taken as the closest prior art. The compounds of claim 5 differ in the identity of the substituent on the aryl group. The structurally closest compounds are ex. 18 and 19, which possess a phenyl ring substituted by a benzyloxy group and a methanesulfonyloxy group, whereas the compounds of D3 may have an aryl group substituted by a hydroxy group, a trifluoromethoxy group or alkoxy group. In the absence of any teaching that the substituents of present claim 5 and those of D3 are equivalent in compounds with PPAR modulating activity, it does not appear to be obvious to provide further compounds with this activity by modifying the compounds of D3 in the way claimed. Thus the compounds of claim 5 which fall within the scope of claim 1 and which have the alleged activity may be considered inventive.

Claims 1-4 and 6-11 do not fulfil the requirements of Article 33(3) PCT.

Claim 5 fulfils the requirements of Article 33(3) PCT

Industrial applicability

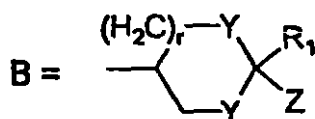
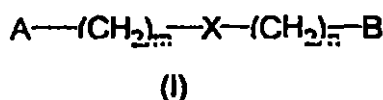
Claims 1-6 and 11 fulfil the requirements of Article 33(4) PCT.

No unified criteria exist in the PCT Contracting States for assessing whether present claims 7-10 are industrially applicable. The patentability can be dependent upon the formulation of the claims. For example, the EPO does not consider claims to the use of a compound in medical treatment to be industrially applicable, but allows claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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We claim:

1 A compound of formula (I)



5 their tautomeric forms, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, pharmaceutical compositions containing them, wherein 'A' represents optionally substituted, single or fused aryl, cycloalkyl group or an optionally substituted heteroaryl or an optionally substituted heterocyclyl group; 'm' = 0-2; 'n' = 3-6; 'X' represents O, S, -N(R_a)- or -CH₂-; R_a represents H, linear or branched, group
10 selected from alkyl, acyl or aryl, aralkyl group, which may optionally be substituted; 'Y' at each occurrence independently represent O or S; R₁ represents H, linear or branched substituted or unsubstituted alkyl; r = 0-2; Z represents -(CH₂)_sCOOH, alkoxycarbonyl, hydroxymethyl, -CN, substituted or unsubstituted tetrazoles, alkylcarbonyl groups, s = 0-4; with the proviso that when 'X' = CH₂ and

15 i) 'A' represents substituted aromatic heterocyclic group, the substitutions on 'A' does not represent aryl, aromatic, heterocyclic or cycloalkyl group; and
ii) 'A' represents substituted aryl group, the substituent on 'A' represents alkylsulfonyloxy, aryloxy, aralkoxy, cycloalkyl, heteroaryl or heterocyclic group.

20 2. A compound as claimed in claim 1 wherein, when 'A' is substituted, suitable substitutions on 'A' may be selected from hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from amidino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, acyl, acyloxy, acylamino,
25 monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkylsulfonylamino, alkylsulfonyloxy, alkoxycarbonylamino,
30 aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino,

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AMENDED SHEET

REPORTE PRELIMINAR**INTERNACIONAL SOBRE**

Solicitud Internacional No.

PATENTABILIDAD**(HOJA SEPARADA)**

PCT/IN2005/000011

I. Bases del reporte

Las correcciones presentadas con carta fechada 23.9.05 introducen materia objeto que se extienden más allá del contenido de la solicitud como se presentó, contrario al artículo 34(2)(b) PCT. En la descripción original i) excluye los compuestos den donde X es CH₂, A es un grupo heterocíclico sustituido en donde el sustituyente es arilo, aromático, heterocíclico o cicloalquilo. Sin embargo, estos compuestos no se excluyen más. Por lo tanto la actual reivindicación 1 corregida se extiende a los compuestos que no son parte de la descripción original. Adicionalmente la condición corregida i) cantidades para una nueva condición introducida, como es su contenido diferente de aquel en la descripción original. La Oficina Europea de Patentes permite renunciar con base en la solicitud original solo para ser introducido para excluir la materia objeto a partir de una descripción que se considera es una "anticipación accidental". Una descripción se considera es una anticipación accidental si esta no se relaciona con y es remota de la invención reivindicada de tal forma que la persona experta en la técnica nunca podría haberla tomado en consideración cuando realiza la invención. Si

embargo, la condición reivindicada se ha introducido para excluir los compuestos de D1. Este documento se considera es altamente relevante para la evaluación del nivel inventivo ya que este se relaciona con compuestos con la misma actividad. Así una nueva renuncia introducida para excluir los compuestos de D1 no es permisible. Como las correcciones no son permisibles se ha desarrollado el siguiente examen para las reivindicaciones en su forma original.

III. Concepto de sin fundamento

Las reivindicaciones 7-10 se relacionan con la materia objeto considerada por esta Autoridad para ser cubiertas por las provisiones de la regla 67.1(iv)PCT. Por consiguiente, no se formulará concepto con respecto a la aplicabilidad industrial de la materia objeto de estas reivindicaciones (Artículo 34(a)(i)PCT).

Existen 2 reivindicaciones numeradas "3" y no reivindicación 5. el siguiente examen se ha basado en las reivindicaciones en donde la 2ª reivindicación numerada actualmente "3" se trata como la reivindicación 4 y la reivindicación actual 4 se renumera como reivindicación 5.

Un número de ejemplos (3, 12, 17, 26, 35, 37, 48) no caen dentro del alcance de la fórmula (I) de la

reivindicación actual 1. Estos ejemplos se reivindican en la reivindicación 5 por ser los compuestos de las reivindicaciones 1-3. Esto introduce una contradicción dentro de las reivindicaciones, que crea una falta de claridad (Artículo 6 PCT) relacionada con el alcance de las reivindicaciones. Solo la fórmula (I) se ha buscado, así no se establecerá concepto para aquellos compuestos de la reivindicación 5 que no caen dentro de esta fórmula.

V. Declaración motivada

Se hace referencia a los siguientes documentos:

D1: EP-A-1 295 875

D2: Albany Molecular Research, Inc. Technical Reports, vol 7, no 46, 2002, p 8-9

D3: WO00/04011

Novedad

En la reivindicación 1 los compuestos en donde A es entre otros heteroarilo opcionalmente sustituido o heterociclilo opcionalmente sustituido se reivindica. Así es claro que el término "heterociclilo" no incluye heteroarilo - si este lo hizo, ambas posibilidades no se pueden listar separadamente en las reivindicaciones. En la condición i) compuestos en donde A son sustituyentes cicloalquilo o heterocíclicos, aromáticos, o arilo se excluye. No se hace mención de una exclusión de

compuestos en donde A es heteroarilo que tiene estos sustituyentes. D1 describe una fórmula general [1] en donde el grupo que corresponde al A actual es un grupo heterocíclico aromático divalente, es decir un grupo heteroarilo. Esta descripción traslapa con las reivindicaciones actuales. Los compuestos se describen por ser efectivos en triglicéridos inferiores, LDL-C y niveles de insulina en la sangre y puede así ser útil en el tratamiento de entre otros diabetes y obesidad. Adicionalmente D1 describe compuestos específicos que caen dentro del alcance de las actuales reivindicaciones (por ejemplo los compuestos de los ejemplos 1-4). D2 elabora el mecanismo de acción de uno de los compuestos de D1, estableciendo que este es un activador PPAR-alfa selectivo.

Estas descripciones son destructoras de la novedad para las presentes reivindicaciones 1-4 y 6-11. D3 describe la fórmula I general en donde R^2 o R^3 pueden ser arilo (C_6-C_{10}) alquilo (C_1-C_7) en donde el grupo arilo puede opcionalmente ser sustituido. En la reivindicación actual 1, la condición ii) excluye ciertos compuestos en donde A es un grupo arilo sustituido, sin embargo no existe exclusión de compuestos en donde A es un grupo arilo no sustituido. Los compuestos de D3 se describen por ser activadores de PPAR- alfa y gama, útiles como agentes hipolipidémicos e hipoglicémicos. Así la

descripción de D3 traslapa con respecto a las reivindicaciones 1, 3 y 7-10.

Reivindicaciones 1-4, 6-11 no cumplen los requerimientos del Artículo 33(2)PCT.

Nivel inventivo

En vista de su falta de novedad, las reivindicaciones 1-4 y 6-11 no pueden ser inventivas. Re. aquellos compuestos de la reivindicación 5 que caen dentro del alcance de la fórmula (I):

Para aquellos compuestos en donde A es heterocíclico o heteroarilo D1 se toma como la técnica más cercana. Los compuestos de D1 todos tienen dos anillos directamente unidos el uno al otro ((R¹-Het-)). Ninguno de los compuestos de la reivindicación 5 tiene esta característica. No parece ser obvio suministrar compuestos adicionales con actividad moduladora PPAR al reemplazar el anillo R¹ de D1 por uno de los sustituyentes dados en la reivindicación 5. Así para los compuestos en donde A es heterocíclico o heteroarilo, la reivindicación 5 se puede considerar inventiva.

Para los compuestos en donde A es arilo, D3 puede ser tomado como la técnica anterior más cercana. Los compuestos de la reivindicación 5 difieren en la identidad de los sustituyentes en el grupo arilo. Los

()
compuestos estructuralmente más cercanos son ex 18 y 19, que poseen un anillo fenilo sustituido por un grupo benziloxi y un grupo metanosulfoniloxi, mientras que los compuestos de D3 pueden tener un grupo arilo sustituido por un grupo hidroxilo, o un grupo trifluorometoxi o grupo alcoxi. En la ausencia de cualquier enseñanza de que los sustituyentes de la presente reivindicación 5 y aquellos de D3 son equivalentes en compuestos con actividad moduladora PPAR no parece ser obvio suministrar compuestos adicionales con esta actividad al modificar los compuestos de D3 en la forma reivindicada. Así los compuestos de la reivindicación 5 que caen dentro del alcance de la reivindicación 1 y que tienen la actividad alegada se pueden considerar inventivos.

Las reivindicaciones 1-4 y 6-11 no cumplen los requerimientos del Artículo 33(3) PCT.

La reivindicación 5 cumple con los requerimientos del Artículo 33(3) PCT.

Aplicabilidad Industrial

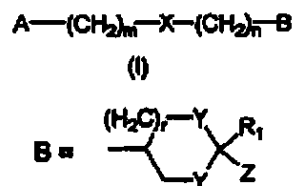
Las reivindicaciones 1-6 y 11 cumplen los requerimientos del Artículo 33(4) PCT.

No existe criterio unificado en los Estados Contratantes del PCT para evaluar si las actuales reivindicaciones 7-10 son aplicables industrialmente. La patentabilidad

puede ser dependiente de la formulación de las reivindicaciones. Por ejemplo, la EPO no considera las reivindicaciones para el uso de un compuesto en el tratamiento médico por ser aplicables industrialmente, pero permite las reivindicaciones para un compuesto conocido para el primer uso en el tratamiento médico y el uso de tal un compuesto para la fabricación de un medicamento para un nuevo tratamiento médico.

Revindicamos

1. Un compuesto de la fórmula (I):



sus forma tautoméricas, sus sales farmacéuticamente
 aceptables, sus solvatos farmacéuticamente aceptables,
 composiciones farmacéuticas que las contienen, en donde
 'A' representa un grupo cicloalquilo, arilo fusionado o
 sencillo opcionalmente sustituido o un grupo
 heterociclico opcionalmente sustituido o heteroarilo
 opcionalmente sustituido; 'm' = 0-2 ; 'n' = 3-6; 'X'
 representa O, S, -N-(Ra)- o -CH₂-; Ra representa H, un
 grupo lineal o ramificado seleccionado de alquilo, acilo
 o arilo, grupo aralquilo, que puede opcionalmente ser
 sustituido; 'Y' en cada ocurrencia representa
 independientemente O o S; R₁ representa H, alquilo
 lineal o ramificado sustituido o no sustituido; r = 0-2;
 Z representa -(CH₂)_sCOOH, alcóxicarbonilo, hidroximetilo,
 -CN, grupos alquilcarbonilo tetrazoles sustituidos o no
 sustituidos, s = 0-4; con la condición que cuando 'X' =
 CH₂ y

i) 'A' representa grupo heterocíclico aromático sustituido, las sustituciones en 'A' no representan un grupo cicloalquilo o heterocíclico, aromático, arilo, y

ii) 'A' representa grupo arilo sustituido, el sustituyente en 'A' representa grupo heterocíclico o heteroarilo, cicloalquilo, aralcoxi, ariloxi, alquilsulfoniloxi.

2. Un compuesto como se reivindica en la reivindicación 1 en donde, cuando 'A' se sustituye, las sustituciones adecuadas en 'A' se pueden seleccionar de grupos hidroxilo, oxo, halo, tio, nitro, amino, ciano, formilo, o grupos sustituidos o no sustituidos seleccionados de amidino, alquilo, haloalquilo, perhaloalquilo, alcoxi, haloalcoxi, perhaloalcoxi, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, bicicloalquilo, bicicloalquenilo, alcoxi, alquenoxi, cicloalcoxi, arilo, ariloxi, aralquilo, aralcoxi, acilo, aciloxi, acilamino, amino monosustituido o disustituido, arilamino, aralquilamino, ácido carboxílico y sus derivados tales como ésteres y amidas, carbonilamino, hidroxialquilo, aminoalquilo, alcoxialquilo, ariloxialquilo, aralcoxialquilo, alquiltio, tioalquilo, ariltio, alquilsulfonilamino, alquilsulfoniloxi, alcoxycarbonilamino, ariloxycarbonilamino, aralquiloxy carbonilamino, aminocarbonilamino,

PATENT COOPERATION TREATY

011

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

To:

SUBRAMANIAM, NATARAJ & ASSOCIATES
Attn. Subramaniam, Nataraj
E 556 Greater Kailash
New Delhi 110 048
INDIA

Received with
Thanks

- 5 JUL 2005

SN&A

(PCT Rule 44.1)

Date of mailing
(day/month/year)

30/06/2005

Applicant's or agent's file reference

ZRC-MC-021

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/IN2005/000011

International filing date
(day/month/year)

07/01/2005

Applicant

CADILA HEALTHCARE LIMITED

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IS/001 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Federico Bonomelli

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

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NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged,
- (ii) the claim is cancelled,
- (iii) the claim is new,
- (iv) the claim replaces one or more claims as filed,
- (v) the claim is the result of the division of a claim as filed

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

- 1 [Where originally there were 48 claims and after amendment of some claims there are 51]
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers, claims 30, 33 and 36 unchanged, new claims 49 to 51 added."
- 2 [Where originally there were 15 claims and after amendment of all claims there are 11]
"Claims 1 to 15 replaced by amended claims 1 to 11."
- 3 [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]
"Claims 1 to 6 and 14 unchanged, claims 7 to 13 cancelled; new claims 15, 16 and 17 added," or
"Claims 7 to 13 cancelled, new claims 15, 16 and 17 added; all other claims unchanged."
- 4 [Where various kinds of amendments are made]
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled, claims 14, 15 and 16 replaced by amended claim 14, claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 48.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference ZRC-MC-021	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/IN2005/000011	International filing date (day/month/year) 07/01/2005	(Earliest) Priority Date (day/month/year) 09/01/2004
Applicant CADILA HEALTHCARE LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (See Box II).

3. ☐ Unity of invention is lacking (see Box III)

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**1,3-DIOXANE DERIVATIVES AND ANALOGUES THEREOF USEFUL IN THE TREATMENT OF I.A.
OBESITY AND DIABETES**

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38 2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant

☐ as selected by this Authority, because the applicant failed to suggest a figure

☐ as selected by this Authority, because this figure better characterizes the invention.

- b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN2005/000011

A. CLASSIFICATION OF SUBJECT MATTER		
IPC 7	C07D405/06 C07D319/06 C07D413/06 C07D495/04 C07D417/06	
	C07D407/06 A61K31/357 A61P3/04 C07D405/12	
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
IPC 7 C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	EP 1 295 875 A (NIPPON SHINYAKU CO., LTD) 26 March 2003 (2003-03-26) cited in the application page 7, line 10 - line 42; claims 1,10	1-4,6-11
X	ASAKI, T. ET AL.: "A novel 1,3-dioxane-2-carboxylic acid derivative, NS-220, as a highly potent and selective PPARalpha agonist." ALBANY MOLECULAR RESEARCH, INC. TECHNICAL REPORTS, vol. 7, no. 46, 2002, pages 8-9, XP002332373 the whole document	1-4,6-10
-/--		
☒ Further documents are listed in the continuation of box C ☒ Patent family members are listed in annex.		
* Special categories of cited documents		
A document defining the general state of the art which is not considered to be of particular relevance		
E earlier document but published on or after the international filing date		
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		
T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention		
X document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone		
Y document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art		
Z document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
17 June 2005		30/06/2005
Name and mailing address of the ISA European Patent Office P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016		Authorized officer Johnson, C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN2005/000011

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document with indication, where appropriate, of the relevant passages	Relevant to claim No
A	WO 00/04011 A (MERCK PATENT GMBH; BERTHELON, JEAN-JACQUES; GUERRIER, DANIEL; RASPE, E) 27 January 2000 (2000-01-27) cited in the application claim 1	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2005/000011

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

- 1 ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 7-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
- 2 ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out specifically
- 3 ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos :
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IN2005/000011

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1295875	A	26-03-2003	AU 5884101 A	03-12-2001
			BR 0111199 A	01-04-2003
			CA 2410382 A1	25-11-2002
			EP 1295875 A1	26-03-2003
			HU 0302397 A2	28-11-2003
			JP 3591514 B2	24-11-2004
			MX PA02011609 A	27-03-2003
			NO 20025659 A	25-11-2002
			UA 72625 C2	15-04-2003
			US 2005009785 A1	13-01-2005
			CN 1430612 A	16-07-2003
			WO 0190087 A1	29-11-2001
			JP 2004250460 A	09-09-2004
			US 2003166697 A1	04-09-2003
			US 2005009892 A1	13-01-2005
			US 2004162325 A1	19-08-2004
			ZA 200209152 A	11-02-2004
WO 0004011	A	27-01-2000	FR 2781222 A1	21-01-2000
			AT 235485 T	15-04-2003
			AU 753287 B2	17-10-2002
			AU 5034799 A	07-02-2000
			BR 9912138 A	10-04-2001
			CA 2337481 A1	27-01-2000
			CN 1309655 A	22-08-2001
			DE 69906303 D1	30-04-2003
			DE 69906303 T2	11-12-2003
			DK 1098893 T3	07-07-2003
			WO 0004011 A1	27-01-2000
			EP 1098893 A1	16-05-2001
			ES 2192853 T3	16-10-2003
			HU 0103411 A2	29-04-2002
			ID 27854 A	26-04-2001
			JP 2002520407 T	09-07-2002
			NO 20010266 A	16-01-2001
			PL 345397 A1	17-12-2001
			PT 1098893 T	29-08-2003
			SI 1098893 T1	31-10-2003
			SK 482001 A3	11-09-2001
			US 6528538 B1	04-03-2003
			ZA 200101303 A	15-05-2002

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To

PCT

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No
PCT/IN2005/000011

International filing date (day/month/year)
07 01 2005

Priority date (day/month/year)
09.01 2004

International Patent Classification (IPC) or both national classification and IPC
C07D405/06, C07D319/06, C07D413/06, C07D495/04, C07D417/06, C07D407/06, A61K31/357, A61P3/04.

Applicant
CADILA HEALTHCARE LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66 1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA



European Patent Office
D-80298 Munich
Tel +49 89 2399 - 0 Tx 523656 epmu d
Fax +49 89 2399 - 4465

Authorized Officer

Johnson, C
Telephone No. +49 89 2399-8287



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No
PCT/IN2005/000011

Box No. I Basis of the opinion

1. With regard to the language this opinion has been established on the basis of the international application, in the language in which it was filed, unless otherwise indicated under this item
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b))
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of
 - a type of material
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b format of material
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IN2005/000011

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos 5(part),7-10

because

☒ the said international application, or the said claims Nos. 7-10 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 5(part) are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 5(part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IN2005/000011

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
Industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	5
	No: Claims	1-4, 6-11
Inventive step (IS)	Yes: Claims	5
	No: Claims	1-4, 6-11
Industrial applicability (IA)	Yes: Claims	1-6, 11
	No: Claims	

2. Citations and explanations

see separate sheet

III. Non-establishment of opinion

Claims 7-10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

There are 2 claims numbered "3" and no claim 5. The following examination has been based on the claims wherein the 2nd claim presently numbered "3" is treated as claim 4 and present claim 4 is renumbered as claim 5.

A number of examples (3, 12, 17, 26, 35, 37, 48) do not fall within the scope of formula (I) of present claim 1. These examples are claimed in claim 5 as being compounds of claims 1-3. This introduces a contradiction into the claims, which creates a lack of clarity (Article 6 PCT) concerning the scope of the claims. Only formula (I) has been searched, thus no opinion will be established for those compounds of claim 5 not falling within this formula.

V. Reasoned statement

Reference is made to the following documents:

D1: EP-A-1 295 875

D2: Albany Molecular Research, Inc. Technical Reports, vol. 7, no. 46, 2002, p. 8-9

D3: WO00/04011

Novelty

In claim 1 compounds wherein A is i.a. optionally substituted heteroaryl or optionally substituted heterocyclyl are claimed. Thus it is clear that the term "heterocyclyl" does not include heteroaryl - if it did, both possibilities would not be separately listed in the claim. In proviso i) compounds wherein A is heterocyclyl having aryl, aromatic, heterocyclic or cycloalkyl substituents are excluded. No mention is made of an exclusion of compounds wherein A is heteroaryl having these substituents. D1 discloses a general formula [1] wherein the group corresponding to the present A is a divalent aromatic heterocyclic group, i.e. a heteroaryl group. This disclosure overlaps with the present claims. The compounds are described as being effective at lowering

triglyceride, LDL-C and insulin levels in the blood and can thus be useful in the treatment of i.a. diabetes and obesity. Furthermore, D1 discloses specific compounds falling within the scope of the present claims (e.g. the compounds of examples 1-4). D2 elaborates on the mechanism of action of one of the compounds of D1, stating that it is a selective PPAR-alpha activator.

These disclosures are novelty-destroying for present claims 1-4 and 6-11.

D3 discloses general formula I wherein R² or R³ may be (C₆-C₁₀)aryl(C₁-C₇)alkyl wherein the aryl group may optionally be substituted. In present claim 1, proviso ii) excludes certain compounds wherein A is a substituted aryl group, however there is no exclusion of compounds wherein A is an unsubstituted aryl group. The compounds of D3 are described as being activators of PPAR-alpha and gamma, useful as hypolipidemic and hypoglycemic agents. Thus the disclosure of D3 overlaps with present claims 1, 3 and 7-10.

Claims 1-4 and 6-11 do not fulfil the requirements of Article 33(2) PCT.

Inventive step

In view of their lack of novelty, claims 1-4 and 6-11 cannot be inventive.

Re. those compounds of claim 5 which fall within the scope of formula (I):

For those compounds wherein A is heterocyclic or heteroaryl, D1 is taken as the closest prior art. The compounds of D1 all have 2 rings directly attached to one another (R¹-Het-). None of the compounds of claim 5 have this feature. It does not appear obvious to provide further compounds with PPAR modulating activity by replacing the R¹ ring of D1 by one of the substituents given in claim 5. Thus for the compounds wherein A is heterocyclic or heteroaryl, claim 5 may be considered inventive.

For the compounds wherein A is aryl, D3 may be taken as the closest prior art. The compounds of claim 5 differ in the identity of the substituent on the aryl group. The structurally closest compounds are ex. 18 and 19, which possess a phenyl ring substituted by a benzyloxy group and a methanesulfonyloxy group, whereas the compounds of D3 may have an aryl group substituted by a hydroxy group, a trifluoromethoxy group or alkoxy group. In the absence of any teaching that the substituents of present claim 5 and those of D3 are equivalent in compounds with PPAR modulating activity, it does not appear to be obvious to provide further compounds with this activity by modifying the compounds of D3 in the way claimed.

Thus the compounds of claim 5 which fall within the scope of claim 1 and which have the alleged activity may be considered inventive

Claims 1-4 and 6-11 do not fulfil the requirements of Article 33(3) PCT.

Claim 5 fulfil the requirements of Article 33(3) PCT.

Industrial applicability

Claims 1-6 and 11 fulfil the requirements of Article 33(4) PCT.

No unified criteria exist in the PCT Contracting States for assessing whether present claims 7-10 are industrially applicable. The patentability can be dependent upon the formulation of the claims. For example, the EPO does not consider claims to the use of a compound in medical treatment to be industrially applicable, but allows claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

55)

SUBRAMANIAM, NATARAJ & ASSOCIATES
ATTORNEYS-AT-LAW
PATENT AND TRADEMARK AGENTS

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ZRC-MC-021

European Patent Office
D-80298 Munich

Germany
(Fax +49 89 2399 4465)

23 September 2005

Authorized officer: Mr. Johnson, C

Dear Sir,

Re: CADILA HEALTHCARE LIMITED
PCT International Application
No. PCT/IN2005/000011
Filed on: 07 January 2005
Priority: 09 January 2004

We refer to the Written Opinion mailed along with Form PCT/ISA/220 on 30 June 2005. The due date for response is 30 September 2005.

The applicants have also considered the Hon'ble Examiner's comments. The applicants are grateful to the Hon'ble Examiner for holding claim 5 to be novel and inventive. The applicants humbly submit herewith the following reply with respect to the other issues raised in ISR and Written Opinion:

The applicants enclose herewith the following:

1. Page 35 of the specification wherein claim 1 has been amended;
2. Comparison document highlighting the exact amendment to Claim 1.

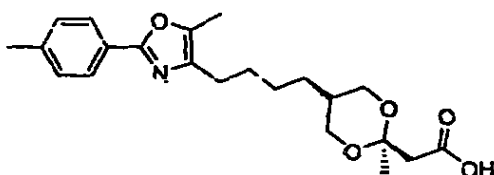
Now referring to the specific cited documents relied upon in the Written Opinion:

Cited documents:

1. **EP 1295875 A (Nippon Shinyaku).**

It is respectfully submitted that the compounds disclosed in this cited document always have two rings directly attached to each other (R1-Het), wherein R1 is aryl, aromatic heterocyclic group or cycloalkyl group; and Het is a divalent aromatic heterocyclic group

Representative compound of the such prior art is



(NS-220)

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On the contrary, it is respectfully submitted that in the compounds disclosed in the applicants' present application, when 'A' represents either a substituted heterocyclic group or a substituted heteroaromatic group, substituents on 'A' does not - according to the amended claim 1 enclosed herewith - include any cyclic group i.e. does not include R1 of the cited document;

Moreover, though the cited document covers various heteroaromatic group in 'Het', all examples as well as specific compounds claimed contain only oxazole group, whereas the applicants' present application describes various heteroaromatic group in 'A'

Thus, it is the applicants' humble submission that the cited document does not teach the compounds of the present invention. Such a modification has not been taught earlier in the literature and by this modification the present inventors have surprisingly obtained compounds with beneficial effect. Moreover, such modifications have been found to affect the selectivity towards the PPAR receptor subtypes (the applicants are in a position to provide data of such selectivity, if the Hon'ble Examiner so requires). Such selectivity has been reported to have beneficial effects in treatment of disease associated with metabolic disorders and reduction of risk factors.

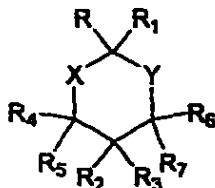
2. Albany Molecular Research Inc, Technical report

This cited document describes a process for preparing NS-220.

NS-220 is covered and disclosed in the earlier cited patent D1). Therefore, the applicants respectfully reiterate the submissions made in connection with D1. Accordingly, the applicants respectfully submit that the disclosure contained in this cited document does not teach or render obvious the compounds claimed in claims 1 to 4 and 6 and 10 of the applicants' present application.

3. WO 200004011 (Merck)

The compounds disclosed in this cited document have the following general structure:



Among the compounds disclosed in this cited document, the compounds, which are of relevance to the present invention are

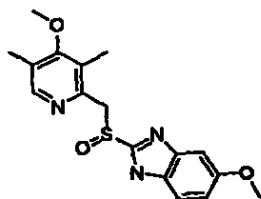
- when one of R₂ and R₃ represents hydrogen, and the other represents (C₆-C₁₀)aryl(C₁-C₇)alkyl;

However, the applicants respectfully submit that in the present invention, when 'A' represents aryl group, the substituents on 'A' are selected from alkylsulfonyloxy, aryloxy, aralkoxy, cycloalkyl, heteroaryl or heterocyclic group only. Such substituents on 'A' are not taught by the cited document. Hence, the compounds claimed by the applicants are novel.

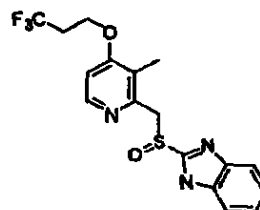
Moreover, with these specific substituents on 'A', the applicants have found out that these compounds show good pharmacological properties (pl. refer to tables 1 & 2 of the present application). The cited document does not provide any supporting pharmacological data substantiating the beneficial effect of the compounds claimed. Also, the compounds of the present invention have surprisingly been found to be more specific modulators of the PPAR subtypes. Accordingly, it is the Applicants' humble submission that these compounds showing surprisingly beneficial properties are not taught by the cited document and hence should be considered patentable over the cited document.

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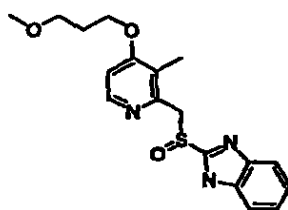
In this context the applicants would like to draw the attention of the Hon'ble Examiner that the mere fact that the only difference appears to be a change of change in substituents on the basic skeleton is not enough reason to hold that the new compound lacks in novelty or inventiveness. The change in the substituents may appear to be simple but what makes such compounds novel and inventive is surprising efficacy they display. As an example we would invite the attention of the Hon'ble Examiner to the following drugs which are already in the market for the same therapeutic category (proton pump inhibitors). If we look closely there is very little modifications of the substituents on the basic ring structure. Yet, all of these compounds have been considered to be patentable inventions



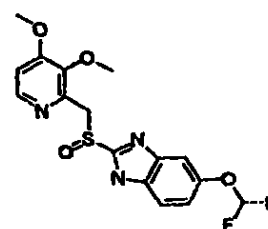
Omeprazole



Lansoprazole



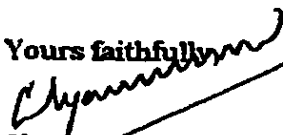
Rabeprazole



Pantoprazole

In view of the above, the applicants respectfully submit that the present invention is inventive over the prior art cited. The applicants respectfully request the Hon'ble Examiner to take the submissions and amendments on record and issue a favourable IPER.

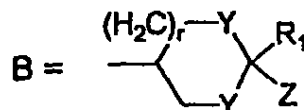
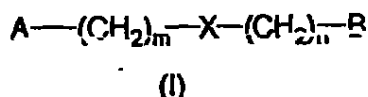
Yours faithfully


Hari Subramaniam

25/

We claim.

A compound of formula (I):

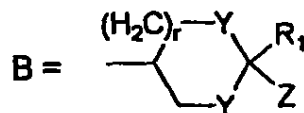
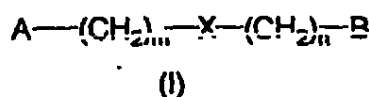


- 5 their tautomeric forms, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, pharmaceutical compositions containing them, wherein 'A' represents optionally substituted, single or fused aryl, cycloalkyl group or an optionally substituted heteroaryl or an optionally substituted heterocyclyl group; 'm' = 0-2; 'n' = 3-6; 'X' represents O, S, -N-(Ra)- or -CH₂-; Ra represents H, linear or branched, group selected from alkyl, acyl or aryl, aralkyl group, which may optionally be substituted;
- 10 'Y' at each occurrence independently represent O or S; R₁ represents H, linear or branched substituted or unsubstituted alkyl; r = 0-2; Z represents -(CH₂)_sCOOH, alkoxycarbonyl, hydroxymethyl, -CN, substituted or unsubstituted tetrazoles, alkylcarbonyl groups, s = 0-4; with the proviso that when 'X' = CH₂ and
- 15 i) 'A' represents substituted aromatic heterocyclic group, the substitutions on 'A' does not represent aryl, aromatic, heterocyclic or cycloalkyl group; and
- ii) 'A' represents substituted aryl group, the substituent on 'A' represents alkylsulfonyloxy, aryloxy, aralkoxy, cycloalkyl, heteroaryl or heterocyclic group.
- 20 2. A compound as claimed in claim 1 wherein, when 'A' is substituted, suitable substitutions on 'A' may be selected from hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from amidino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, acyl, acyloxy, acylamino,
- 25 monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkylsulfonylamino, alkylsulfonyloxy, alkoxycarbonylamino,
- 30 aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino,

25/

We claim:

A compound of formula (I).



- 5 their tautomeric forms, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, pharmaceutical compositions containing them, wherein 'A' represents optionally substituted, single or fused aryl, cycloalkyl group or an optionally substituted heteroaryl or an optionally substituted heterocyclyl group; 'm' = 0-2; 'n' = 3-6, 'X' represents O, S, -N-(R_a)- or -CH₂-; R_a represents H, linear or branched, group selected from alkyl, acyl or aryl, aralkyl group, which may optionally be substituted;
- 10 'Y' at each occurrence independently represent O or S; R₁ represents H, linear or branched substituted or unsubstituted alkyl, r = 0-2; Z represents -(CH₂)_sCOOH, alkoxycarbonyl, hydroxymethyl, -CN, substituted or unsubstituted tetrazoles, alkylcarbonyl groups, s = 0-4; with the proviso that when 'X' = CH₂ and
- 15 i) 'A' represents substituted aromatic heterocyclic group, the substitutions on 'A' does not represent aryl, aromatic, heterocyclic or cycloalkyl group; and
- ii) 'A' represents substituted aryl group, the substituent on 'A' represents alkylsulfonyloxy, aryloxy, aralkoxy, cycloalkyl, heteroaryl or heterocyclic group.
- 20 2. A compound as claimed in claim 1 wherein, when 'A' is substituted, suitable substitutions on 'A' may be selected from hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from amidino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, acyl, acyloxy, acylamino,
- 25 monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkylsulfonylamino, alkylsulfonyloxy, alkoxycarbonylamino,
- 30 aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino,

From the INTERNATIONAL BUREAU

PCTINFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Article 31(1) and Rule 61.3)

To

SUBRAMANIAM, Hanharan
Subramaniam, Nataraj & Associates
E-556, Greater Kailash II
New Delhi - 110 048
INDE

Date of mailing (day/month/year)

27 October 2005 (27.10.2005)

Received with
Thanks

Applicant's or agent's file reference

ZRC-MC-021

- 3 - 2005

IMPORTANT INFORMATION

International application No.
PCT/IN2005/00001

SN&A

International filing date (day/month/year)
07 January 2005 (07 01 2005)Priority date (day/month/year)
09 January 2004 (09 01 2004)

Applicant

CADILA HEALTHCARE LIMITED et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election

EP: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR

National: BG, CA, CN, CZ, DE, JP, KP, KR, MN, NO, PL, RO, RU, SK, SM, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

AP: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW

EA: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

OA: BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

National: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BR, BW, BY, BZ, CH, CO, CR, CU, DK, DM, DZ, EC, EE, EG,
ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,MG, MK, MW, MX, MZ, NA, NI, NZ, OM, PG, PH, PT, SC, SD, SE, SG, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
UG, UZ, VC, VN, YU, ZA, ZM, ZW

3. Since the election(s) was (were) made before the expiration of 19 months from the priority date, the applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fees and furnishing, as prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary report on patentability (Chapter II of the Patent Cooperation Treaty) (Article 34.3(b) and Rule 74.1).

Some Offices have fixed time limits expiring later than the above-mentioned time limit. See the Annex to Form PCT/IB/101 and for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters, the PCT Newsletter and the WIPO Internet site, updated regularly.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Dorothee Mülhausen

Facsimile No. +41 22 740 14 35

Facsimile No. +41 22 338 87 40

PATENT COOPERATION TREATY

WO 2005/077943
PCT/IN2005/000011

From the INTERNATIONAL BUREAU

PCT

FIRST NOTICE INFORMING THE APPLICANT OF
THE COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED) OFFICES WHICH
DO NOT APPLY THE 30 MONTH TIME LIMIT
UNDER ARTICLE 22(1))

(PCT Rule 47 (c))

To

SUBRAMANIAM, Hanharan
Subramaniam, Nataraj & Associates
5-656, Greater Kailash II
New Delhi 110048

NOTE with
Thanks

2005

SN&A

IMPORTANT NOTICE

Date of mailing (day/month/year)

01 September 2005 (01 09 2005)

Applicant's or agent's file reference

ZRC-MC-021

International application No

PCT/IN2005/000011

International filing date (day/month/year)

07 January 2005 (07 01 2005)

Priority date (day/month/year)

09 January 2004 (09 01 2004)

Applicant

CADILA HEALTHCARE LIMITED et al

ATTENTION For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date) does apply, please see Form PCT/IB/308(Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date)

- 2 Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does not apply, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis 1. The International Bureau has effected that communication on the date indicated below:
25 August 2005 (25 08 2005)

CH

In accordance with Rule 47 (c) (ii) those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s)

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, does not apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis 1:

LU, SE, TZ, UG, ZM

In accordance with Rule 47 (c) (i) those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application

4. **TIME LIMITS** for entry into the national phase

For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of 19 months from the priority date (see Article 39(1)) the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 20 MONTHS from the priority date

In practice, time limits other than the 20-month time limit will continue to apply for various periods of time in respect of certain of the designated Offices listed above. For regular updates on the applicable time limits (20 or 21 months or other time limit) Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site at <http://www.wipo.int/pct/en/index.html>

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34 chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No +41 22 740 14 55

Authorized officer

Dorothee Mülhausen

Facsimile No +41 22 338 87 40

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From the INTERNATIONAL BUREAU

PCT**NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT**

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 07 July 2005 (07 07 2005)	To SUBRAMANIAM, Hartharan Subramaniam Nataraj & Associates 1-556, Greater Kailash-II New Delhi - 110 048 INDIA Received with Thanks - 1 AUG 2005
Applicant's or agent's file reference ZRC-MC-021	NOTIFICATION
International application No PCT/IN2005/000011	International filing date (day/month/year) 07 January 2005 (07 01 2005)
International publication date (day/month/year)	Priority date (day/month/year) 09 January 2004 (09 01 2004)
Applicant CADILA HEALTHCARE LIMITED et al	

1 By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR" in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2 (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3 (If applicable) An asterisk (*) appearing next to a date of receipt in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b) the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
09 January 2004 (09 01 2004)	23/MUM/2004	IN	07 May 2005 (19.05 2005)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Kishan SINGH RAM
Facsimile No +41 22 338 82 70	Facsimile No (41-22) 338 87 40
	Telephone No +41 22 338 8450

PATENT COOPERATION TREATY

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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF RECEIPT
OF SEARCH COPY

(PCT Rule 25.1)

To:

SUBRAMANIAM, NATARAJ & ASSOCIATES
Attn. Subramaniam, Hariharan
E 556 Greater Kailash II
New Delhi 110 048
INDIAReceived with
Thanks

16 Jun 2005

Date of mailing
(day/month/year)

09/06/2005

Applicant's or agent's file reference

SNA

ZRC-MC-021

IMPORTANT NOTIFICATION

International application No.

PCT/IN2005/000011

International filing date (day/month/year)

07/01/2005

Priority date (day/month/year)

09/01/2004

Applicant

CADILA HEALTHCARE LIMITED

1. Where the International Searching Authority and the receiving Office are not the same office:

The applicant is hereby notified that the search copy of the international application was received by this International Searching Authority on the date indicated below

Where the International Searching Authority and the receiving Office are the same office:

The applicant is hereby notified that the search copy of the international application was received on the date indicated below.

19/05/2005 (date of receipt).2. ☐ The search copy was accompanied by a nucleotide and/or amino acid sequence listing or tables related thereto in computer readable form.

3. Time limit for establishment of international search report and written opinion of the International Searching Authority

The applicant is informed that the time limit for establishing the international search report and the written opinion of the International Searching Authority is three months from the date of receipt indicated above or nine months from the priority date, whichever time limit expires later (Rules 42.1 and 43bis.1(a))

4. A copy of this notification has been sent to the International Bureau and, where the first sentence of paragraph 1 applies, to the receiving Office.

Name and mailing address of the International Searching Authority

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

ISA/EP

From the INTERNATIONAL BUREAU

PCT

SECOND AND SUPPLEMENTARY NOTICE
INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES
WHICH APPLY THE 30 MONTH TIME
LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E-556 Greater Kailash II
New Delhi - 110 048
INDE

Date of mailing (day/month/year)

11 May 2006 (11.05 2006)

Applicant's or agent's file reference
ZRC-MC-021

IMPORTANT NOTICE

International application No.
PCT/IN2005/000011International filing date (day/month/year)
07 January 2005 (07 01 2005)Priority date (day/month/year)
09 January 2004 (09 01 2004)

Applicant

CADILA HEALTHCARE LIMITED et al

ATTENTION For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does not apply, please see Form PCT/IB/308(First Notice) issued previously

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, has/have requested that the communication of the international application, as provided for in Article 20 be effected under Rule 93bis.1 The International Bureau has effected that communication on the date indicated below
25 August 2005 (25.08.2005)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, MZ, NA, PG, RU, SY, TM, US

In accordance with Rule 47.1(c-bis)(ii), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002 does apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BW, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KZ, LC, LK, LR, LS, LT, LV, MA, MG, MN, MW, MX, NL, NO, NZ, OA, OM, PH, PL, PT, RO, SC, SD, SG, SK, SL, SM, TJ, TN, TR, TT, UA, UZ, VC, VN, YU, ZA, ZW

- In accordance with Rule 47.1(c-bis)(iii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

TIME LIMITS for entry into the national phase

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date.

In practice, time limits other than the 30-month time limit will continue to apply for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For regular updates on the applicable time limits (30 or 31 months or other time limits), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Dorothee Mülhausen

Facsimile No +41 22 740 14 35

Facsimile No +41 22 338 87 40

Form PCT/IB/308/Second and Supplementary Notice (January 2004)

Expediente No			No de Folio
Item		No de unidades	
1	CD		✓
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA	2	✓
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS		

Observaciones: este Fm

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

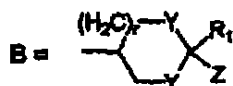
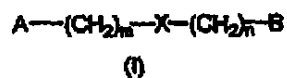
09/08/06

1) SOLICITUD DE:			
☒ Patente de invención		☐ Patente de Modelo de Utilidad	
☐ Capitulo I		☒ Capitulo II.	
2) SOLICITANTE (71)	Nombre: CADILA HEALTHCARE LIMITED Dirección: Zydus Tower, Satellite Cross Road, Ahmedabad 380 015, Gujarat, India Nacionalidad o domicilio: Gujarat, India Lugar de constitución: India		IDENTIFICACIÓN C.C. ☐ NIT: ☐ C.E. ☐ OTRO ☐ NÚMERO Cual _____
	Teléfono: _____ Fax: _____ E. Mail: _____		
3) REPRESENTANTE O APODERADO	Nombre: DILIA MARIA RODRIGUEZ D'ALEMAN Dirección: Carrera 11 N°. 86-53 Piso 6 Bogotá D.C. Teléfono: 6181088 Fax: 6350824 E. Mail: info@clarkemodet.com.co		IDENTIFICACIÓN C.C. ☒ NIT: ☐ C.E. ☐ OTRO ☐ NÚMERO: 41.654.882 TP: 20824 CSJ
4) INVENTOR (ES) (72)	Nombre: 1. LOHRA, Braj, Bhushan; 2. LOHRA, Vidya, Bhushan. Dirección: 1 y 2 . Cadila Healthcare Limited, Zydus Tower, Satellite Cross Road, Ahmedabad 380 015, Gujarat, India Nacionalidad o Domicilio: 1 y 2 Hindúes		
5) PCT (86) Solicitud Internacional No. PCT/IN2005/000011 Fecha: Enero 7, 2005 Publicación Internacional No. WO2005/077943 A1 Fecha: Agosto 25, 2005			
6) Título (54) DERIVADOS DE 1, 3 – DIOXANO Y ANÁLOGOS DE ÉSTOS ÚTILES EN EL TRATAMIENTO DE OBESIDAD Y DIABETES ENTRE OTROS			
7) Clasificación Internacional: C07D 405/06, 319/06, 413/06, 495/04, 417/06, 407/06, A61K 31/357, A61P 3/04, C07D 405/12			
8) PRIORIDAD	33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI ☒ NO ☐	India	Enero 9, 2004	23/MUM/2004
9) Comprobante de pago N° 06-54-185 Fecha: Julio 17 de 2006			
Instrucciones para el diligenciamiento del presente formulario Ver reverso de esta pagina			

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Revindicamos

1. Un compuesto de la fórmula (I):



sus forma tautoméricas, sus sales farmacéuticamente aceptables, sus solvatos farmacéuticamente aceptables, composiciones farmacéuticas que las contienen, en donde 'A' representa un grupo cicloalquilo, arilo fusionado o sencillo opcionalmente sustituido o un grupo heterociclilo opcionalmente sustituido o heteroarilo opcionalmente sustituido; 'm' = 0-2 ; 'n' = 3-6; 'X' representa O, S, -N-(Ra)- o -CH₂-; Ra representa H, un grupo lineal o ramificado seleccionado de alquilo, acilo o arilo, grupo aralquilo, que puede opcionalmente ser sustituido; 'Y' en cada ocurrencia representa independientemente O o S; R₁ representa H, alquilo lineal o ramificado sustituido o no sustituido; r = 0-2; Z representa -(CH₂)_sCOOH, alcoxycarbonilo, hidroximetilo, -CN, grupos alquílcarbonilo tetrazoles sustituidos o no sustituidos, s = 0-4; con la condición que cuando 'X' = CH₂ y

i) 'A' representa grupo heterocíclico aromático sustituido, las sustituciones en 'A' no representan un grupo cicloalquilo o heterocíclico, aromático, arilo, y

ii) 'A' representa grupo arilo sustituido, el sustituyente en 'A' representa grupo heterocíclico o heteroarilo, cicloalquilo, aralcoxi; ariloxi, alquilsulfoniloxi.

2. Un compuesto como se reivindica en la reivindicación 1 en donde, cuando 'A' se sustituye, las sustituciones adecuadas en 'A' se pueden seleccionar de grupos hidroxilo, oxo, halo, tio, nitro, amino, ciano, formilo, o grupos sustituidos o no sustituidos seleccionados de amidino, alquilo, haloalquilo, perhaloalquilo, alcoxi, haloalcoxi, perhaloalcoxi, alqueno, alquino, cicloalquilo, cicloalqueno, bicicloalquilo, bicicloalqueno, alcoxi, alqueno, cicloalcoxi, arilo, ariloxi, aralquilo, aralcoxi, acilo, aciloxi, acilamino, amino monosustituido o disustituido, arilamino, aralquilamino, ácido carboxílico y sus derivados tales como ésteres y amidas, carbonilamino, hidroxialquilo, aminoalquilo, alcoxialquilo, ariloxialquilo, aralcoxialquilo, alquiltio, tioalquilo, ariltio, alquilsulfonilamino, alquilsulfoniloxi, alcoxycarbonilamino, ariloxycarbonilamino, aralquiloxy carbonilamino, aminocarbonilamino,

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION

☒

MODELO DE UTILIDAD ☐

- ◆ Indicación de que se solicita la concesión de una patente ☒
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ Dibujos de ser estos pertinentes ☒
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☐

INCOMPLETA ☐

DISEÑO INDUSTRIAL ☐

- ◆ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

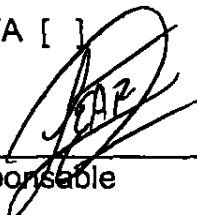
INCOMPLETA ☐

ESQUEMA DE TRAZADO ☐

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐


Firma Responsable

Fecha Agosto 09 de 2006.

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120

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
RODRIGUEZ DILIA MARIA
Apoderado(a) y/o Representante de
CADILA HEALTHCARE LIMITED

REFERENCIA	Radicación No.	06 078216
	Solicitud internacional	IN2005/000011
	Fecha inicio fase nacional	09/08/2006
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	11211

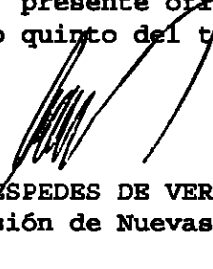
Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

2. Debe aclarar o presentar un nuevo capítulo reivindicatorio, por cuanto el aportado con la solicitud presenta deficiencias en su numeración.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha _____ aalvarado 06 OCT. 2006