

75 79

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

SUPERINDUSTRIA Y COMERCIO
Radicacion : 01011989 00000003 Folios: 88
Fecha (RND): 2001-05-30 16:46:42
Tramite : 002 PATENTES D 1 REGISTRO/ 444 RESPUESTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: P1.-MERCK & CO, INC.-Solicitud de Patente de Invención para
"ACIDOS ARILOXIACETICOS PARA LA DIABETES Y
DESOREDENES DE LIPIDOS".-Clase A. 61-Expediente
número 01-011.989.-

1. Me refiero a mi memorial de 22 de Marzo de 2001 y al requerimiento hecho por ese Despacho notificado por fijación en lista de fecha 5 de Abril del mismo año.

2. Anexos me permito presentar a usted:

- (1) En original y dos copias, una de ellas de 6cm x 6cm, Arte Final de la formula química característica de la Invención para la publicación en la Gaceta de la Propiedad Industrial;
- (2) Copia autentica, debidamente certificada de la solicitud de patente presentada para el invento arriba nombrado **respecto de la cual reclamo prioridad**, a saber la solicitud estadounidense número 60/183.593 de 18 de Febrero de 2000, junto con su traducción correspondiente a las legalizaciones y reivindicaciones de dicho documento; y
- (3) Documento que acredita el traspaso que los autores del invento de la referencia hacen a favor de mi representando, de sus derechos sobre el mismo, debidamente apostillado, junto con su traducción oficial número 054-2001, debidamente legalizada

76

hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 421018 de 27 de Marzo de 2001 correspondiente a las legalizaciones y partes pertinentes de dicho documento de traspaso.

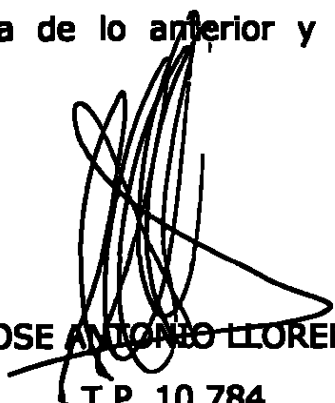
3. Llamo la atención de ese Despacho al hecho que el arte final no fue requerido pero va a ser presentado junto con este memorial.

4. Anexo también me permito acompañar copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial del señor Gabriel Rueda Chadid quien elaboró la traducción de las legalizaciones y las reivindicaciones de la solicitud estadlnense número 60/183.593 de 18 de Febrero de 2000.

5. Anexo también me permito acompañar Comprobante de Pago número 33.132, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa de tramitación correspondiente al excedente de palabras que contiene el extracto que debe aparecer en la Gaceta de la Propiedad Industrial en relación con la presente solicitud.

6. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,



JOSE ANTONIO LLOREDA

T.P. 10.784

Código 231

Exp. 01-011.989
77

Industria y Comercio
SUPERINTENDENCIA

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 1 - 33,132
FECHA : MAYO 25 DE 2001

C O P I A

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
LOREDA Y CIA S. A	CONSIGNACION	BANCO POPULAR	050-00110-6	4029888	25/05/2001	3,984,820.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
201	50005-01-01	SOLICITUDES	9 POR PALABRA ADICIONAL (A PARTIR D
			TOTAL : \$ 108,540.00

SON: CIENTO OCHO MIL QUINIENTOS CUARENTA PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

Expediente No		No de Follo
Item	01011989 No de unidades	
1	CD	
2	DVD	
3	REVISTA	
4	LIBRO	
5	PERIODICO	
6	DISQUETES	
7	SOBRE DE MANILA	✓
8	SOBRE BLANCO TAMAÑO CARTA	
9	SOBRE BLANCO TAMAÑO OFICIO	
10	OTROS:	
Observaciones: ante final.		

79

EL SUSCRITO JEFE DEL AREA DE
LEGALIZACIONES DE MINISTERIO DE
RELACIONES EXTERIORES.

HACE CONSTAR

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
15 DIC 2000

Que el señor Gabriel Rueda, se encuentra debidamente
registrado ante este Ministerio, como traductor e
intérprete oficial para los idiomas INGLÉS -ESPAÑOL,
ESPAÑOL - INGLÉS.

Para efectos de esta certificación el interesado presentó
copia autenticada de la resolución del Ministerio de
Justicia acerca de la vigencia de la resolución 1566
1982.

HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA

Dada en Santafé de Bogotá, D. C., a los nueve días
(19) del mes de diciembre de 1998.

Neibón Sánchez Torres
Jefe Área de Legalizaciones

NST/ptm.

COMO NOTARIO SEXTO ENCARGADO DEL CIRCULO
DE SANTAFE DE BOGOTA HAGO CONSTAR QUE
ESTA COPIA FOTOSTATICA CONCORDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA
01 JUL 1998

01 SET 2000

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
15 DIC 2000



Ministerio de Justicia y del Derecho

EL SECRETARIO GENERAL DEL MINISTERIO DE JUSTICIA Y DEL DERECHO

CERTIFICA:

Que por Resolución 5996 del 29 de noviembre de 1982, le fue expedida licencia para ejercer funciones de Traductor e Intérprete Oficial en los idiomas INGLES-ESPAÑOL, ESPAÑOL-INGLES a GABRIEL RUEDA CHADID, identificado con la cédula No. 17.124.145 expedida en Bogotá. Que dicha resolución encuentra vigente en la fecha.

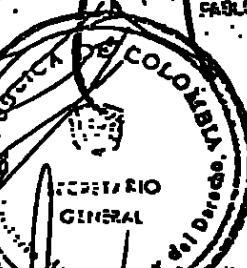
A solicitud del interesado, en Santa Fe de Bogotá, el mes de noviembre de 1994.

JORGE LOIS SAROGAL SAROGAL

COMO NOTARIO SEXTO DE SANTIAGO DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
13 JUL 2000

COMO NOTARIO SEXTO DE SANTIAGO DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
21 FEB 2001

COMO NOTARIO SEXTO DE SANTIAGO DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
1450.1998



COMO NOTARIO SEXTO DE SANTIAGO DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
01 SET 2000

COMO NOTARIO SEXTO DE SANTIAGO DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
13 JUL 2000

81 &

TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL DE SANTAFÉ DE BOGOTÁ
SECRETARÍA GENERAL

LA SUSCRITA SECRETARÍA DEL H. TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL
DE SANTAFÉ DE BOGOTÁ,

COMO NOTARIO SEYTO DE
SANTAFÉ DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTÉNTICA QUE HE TENIDO A LA VISTA
SANTAFÉ DE BOGOTÁ
3 OCT 2000

CERTIFICA:

Que el Acuerdo No. 183 de diciembre 3 de 1982 emanado de esta Corporación, por medio del cual dió posesión a **GABRIEL RUEDA CHADID** identificado con Cédula de Ciudadanía No. 124.145 de Bogotá como **TRADUCTOR E INTERPRETE OFICIAL EN ESPAÑOL-INGLÉS**, en virtud de la Resolución No. 5996 de 1998 se encuentra **VIGENTE**.

COMO NOTARIO SEYTO DE
SANTAFÉ DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTÉNTICA QUE HE TENIDO A LA VISTA
SANTAFÉ DE BOGOTÁ
21 FEB 2000
PABLO MENDEZ BARAJAS

COMO NOTARIO SEYTO DE
SANTAFÉ DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTÉNTICA QUE HE TENIDO A LA VISTA
SANTAFÉ DE BOGOTÁ
07 SET 2000
21 AGO 1998

Se expide en Santafé de Bogotá D.C., a dieciseis (16) de noviembre
mil novecientos noventa y cuatro (1994).

[Signature]
MARIA INES RODRIGUEZ TORRES
SECRETARIA

COMO NOTARIO SEYTO DE
SANTAFÉ DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTÉNTICA QUE HE TENIDO A LA VISTA
SANTAFÉ DE BOGOTÁ
01 JUL 1998
JUAN MANUEL ESTENO MEDINA
NOTARIO
PABLO MENDEZ BARAJAS
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTÉNTICA QUE HE TENIDO A LA VISTA
SANTAFÉ DE BOGOTÁ
12 NOV 1998

COMO NOTARIO SEYTO DE
SANTAFÉ DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTÉNTICA QUE HE TENIDO A LA VISTA
SANTAFÉ DE BOGOTÁ
08 SET 1998
PABLO MENDEZ BARAJAS

crm. /

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Marck & Co., Inc. C-206304

REF: LLC-0023-2001. La presente es Traducción Oficial de un documento presentado originalmente en inglés. Esta traducción es elaborada por Gabriel Rueda Chadid (Traductor Oficial).

ESTADOS UNIDOS DE AMERICA

A TODOS AQUELLOS QUE LLEGAREN A LEER EL CONTENIDO DEL

PRESENTE DOCUMENTO LES CERTIFICAMOS:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Marcas y Patentes de los Estados Unidos

Noviembre 17, 2000

Se certifica que anexo se encuentra fiel copia de los Registros de la Oficina de Marcas y Patentes de los Estados Unidos correspondientes a los documentos de la patente solicitada y cuya identificación aparece más adelante, la cual cumplió con los requerimientos exigidos para que se otorgue una fecha de presentación de acuerdo con los dispuesto en la Sección 35 USC 111.

Número de Solicitud: 80/183.593

Fecha de presentación: Febrero 18, 2000

Por autorización del

COMISIONADO DE MARCAS REGISTRADAS Y PATENTES

W. MONTGOMERY

Funcionario Encargado de Certificaciones (Hay firma y sello)

GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 1996 DE NOV. 19-93
MINISTERIO DE JUSTICIA

83 82

Oficina de Marcas y Patentes:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Indicar con un signo (+) dentro de esta casilla —> +

PORTADA PARA LA SOLICITUD PROVISIONAL DE PATENTES

La presente solicitud de presentación de solicitud provisional de acuerdo con 37 CFR 1.53 (c)

Expediente No.: 20630PV

INVENTOR(ES)/SOLICITUD(ES)

Apellido	Primer Nombre	Lugar de Residencia (Ciudad y Estado o País)
Kun	Liu	Edison, New Jersey
Libo	Xu	Dayton, New Jersey
Phieng	Siliphaivanh	Chapel Hill, North Carolina
A. Brian	Jones	Westfield, New Jersey

TITULO DEL INVENTO (280 caracteres máximo)

ACIDOS ARILOXIACETICOS PARA DIABETES Y DESORDENES DE LIPIDOS

DIRECCION DE CORRESPONDENCIA

Merck & Co., Inc.

Patent Department - RY60-30

P.O.Box 2000

X Cliente No. 000210

Rahway

Estado: New Jersey

Código: 07065

País: USA

PARTES ADJUNTAS DE LA SOLICITUD (indicar lo que se aplica)

X Especificaciones Número de Páginas: 49

FORMA DE PAGO (Indicar)

X El Comisionado queda autorizado para cobrar los derechos de presentación y acreditar la cuenta No. 13-2755

82
84

DERECHOS PROVISIONALES DE PRESENTACION:

\$ 150.00

Fue elaborado por una entidad del Gobierno de los Estados Unidos, o bajo contrato con entidades del Gobierno de dicho país

___ No. ___ Si.

Firmado,

Fecha: 02/18/2000

NOMBRE: JAMES L. McGINNIS

TELEFONO: 732-594-0641

No. de Registro: 34.387

CERTIFICADO DE ENVIO POR CORREO EXPRESO

Fecha del Envío: Febrero 18, 2000

No. de Etiqueta de Correo Expreso: EL520789833US

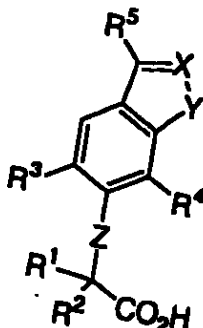
Certifico que los siguientes documentos en relación con la solicitud mencionada fueron depositados en el servicio postal de los Estados Unidos, correo Expreso "Oficina Postal al Destinatario" en Washington, D.C. 20231.

(Hay firma)

Fecha: Febrero 18, 2000.

GABRIEL RUEDA CHADIA
TRADUCTOR OFICIAL
RESOLUCION 1996 DE NOV. 29-83
MINISTERIO DE JUSTICIA

1. Un compuesto que tiene la fórmula I:



y sus sales, precursores de drogas farmacéuticamente aceptables, donde

R¹ y R² se seleccionan cada uno independientemente del grupo conformado por H, F, alquilo C₁₋₅, alquenilo C₂₋₅, y alquinilo C₂₋₅, donde los mencionados alquilo, alquenilo y alquinilo pueden ser lineales o bifurcados y sustituidos opcionalmente por 1-3 átomos de halógeno; u opcionalmente R¹ y R² conjuntamente forman un cicloalquilo C₃₋₅;

R³ y R⁴ se selecciona cada uno independientemente del grupo conformado por alquilo C₁₋₅, alquenilo C₂₋₅, alquinilo C₂₋₅, y cloro, con la condición de que R³ y R⁴ no sean ambos cloro, donde los mencionados grupos alquilo, alquenilo, y alquinilo pueden ser lineales o bifurcados, sustituyéndose opcionalmente por 1-5 átomos de flúor;

X es N o CR;

Y es O, S, o NR;

Z es O o S;

Cada R se selecciona independientemente del grupo conformado por H, alquilo C₁₋₅, alquenilo C₂₋₅, y alquinilo C₂₋₅, donde los mencionados alquilo, alquenilo y alquinilo pueden ser lineales o bifurcados y opcionalmente sustituidos por 1-5 átomos de flúor y/o un -OalquiloC₁₋₅, donde el mencionado -OalquiloC₁₋₅ es sustituido opcionalmente por 1-7 átomos de flúor; y

R^B se selecciona a partir del grupo conformado por H, alquilo C₁₋₅, alquenilo C₂₋₅, alquinilo C₂₋₅, Arilo C₆₋₁₀, -OalquiloC₁₋₅, -OalqueniloC₂₋₅, -OalquiniloC₂₋₅, -OAriloC₆₋₁₀, Cicloalquilo C₃₋₆, Heterociclilo de 5-6 miembros, Heteroarilo de 5-6 miembros, -OCicloalquilo C₃₋₆, -O Heterociclilo de 5-6 miembros, -O Heteroarilo de 5-6 miembros, y el grupo alquilo C₁₋₄ que comprende en la posición "a" la interrupción de la cadena o al final de ésta un grupo que se selecciona a partir de Arilo C₆₋₁₀, Cicloalquilo C₃₋₆, Heterociclilo de 5-6 miembros, y Heteroarilo de 5-6 miembros, donde cada uno de los mencionados alquilo, alquenilo, alquinilo, -Oalquilo, -Oalquenilo, y -Oalquinilo, se sustituye opcionalmente por 1-5 átomos de flúor y/o un grupo -OCH₃ o -OCF₃, y cada uno de los mencionados grupos Arilo, Cicloalquilo, Heteroaril, Heterociclilo, -OArilo, -OCicloalquilo, -OHeteroarilo, y -OHeterociclilo, se sustituye opcionalmente por 1-7 átomos de halógeno y/o un grupo -OCH₃ o -OCF₃.

2. Un compuesto que tiene la formula I según se describió en la Reivindicación 1, donde X es N y Y es O.

9/
87

3. Un compuesto que tiene la formula I según se describió en la Reivindicación 1, donde X es N y Y es S.

4. Un compuesto que tiene la formula I según se describió en la Reivindicación 1, donde X es N y Y es NR.

5. Un compuesto que tiene la formula I según se describió en la Reivindicación 1, donde X es CR y Y es O.

6. Un compuesto que tiene la formula I según se describió en la Reivindicación 1, donde X es CR y Y es S.

7. Un compuesto que tiene la formula I según se describió en la Reivindicación 1, donde X es CR y Y es NR.

8. Un compuesto que tiene la formula I según se describió en una de las Reivindicaciones 2 a 7, donde

R⁵ se selecciona a partir del grupo conformado por H, alquilo C₁₋₅, alquenilo C₂₋₅, alquinilo C₂₋₅, -OalquiloC₁₋₅, -OalqueniloC₂₋₅, -OalquiniloC₂₋₅, y fenoxi, donde los mencionados alquilo, alquenilo, alquinilo -Oalquilo, -Oalquenilo, y -Oalquinilo se sustituyen opcionalmente por 1-5 átomos de flúor, y donde el fenoxi es sustituido opcionalmente por 1-5 halógenos.

9. Un compuesto según se describió en la Reivindicación 8, donde

R¹ y R² son cada uno H o alquilo C₁₋₅, donde el número de átomos de carbono en R¹ y R² conjuntamente es 0-5,

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R^3 y R^4 son cada uno y de manera independiente alquilo C_{1-5} ;

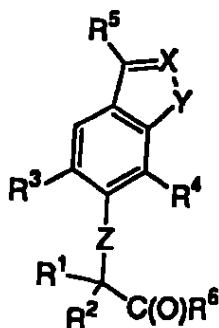
R^5 se selecciona a partir del grupo conformato por alquilo C_{1-5} y -Oalquilo C_{1-5} , donde el mencionado alquilo y -Oalquilo son sustituidos opcionalmente por 1-5 átomos de flúor, y

Z es O.

10. Un compuesto según se describió en la Reivindicación 9, donde R_5 es alquilo C_{1-5} , -Oalquilo C_{1-5} , CF_3 , C_2F_5 , $-OCF_3$ o $-C_2F_5$; y

R^3 y R^4 son cada uno n-propilo.

11. Un compuesto que tiene la formula Ia,



Ia

donde R^6 es un grupo que se remueve fácilmente bajo condiciones fisiológicas durante o después de la administración a un paciente mamífero para lograr un compuesto que tenga la formula I, o su anion carboxilato, o una de sus sales farmacéuticamente aceptables, según se describe en la Reivindicación 1; y

83
89

donde R^1 , R^2 , R^3 , R^4 , R^5 , X, Y, Z, y R corresponden a las definiciones dadas en la Reivindicación 1.

12. Un compuesto según se describió en la Reivindicación 11, donde R^6 se selecciona a partir del grupo conformado por $-OR^7$, $-OCH_2OR^7$, $-OCH(CH_3)OR^7$, $-OCH_2OC(O)R^7$, $-OCH(CH_3)OC(O)R^7$, $-OCH_2OC(O)OR^7$, $-OCH(CH_3)OC(O)OR^7$, $-NR^8R^9$, y $-ONR^8R^9$.

donde cada R^7 se selecciona independientemente a partir de alquilo C_1 -e sustituido opcionalmente por uno o dos grupos que se seleccionan a partir de $-CO_2H$, $-CONH_2$, $-NH_2$, $-OH$, $-OAc$, $NHAc$, y fenilo; y

donde cada R^8 se selecciona independientemente a partir de H y R^7 .

13. Un compuesto representado por cualquiera de las estructuras de los Ejemplos 1-29.

14. Una composición farmacéutica que comprende un compuesto de una de las Reivindicaciones 1-13 y un portador farmacéuticamente aceptable.

15. Un método para el tratamiento, control o prevención de la diabetes mellitus (Tipo 2) no insulino dependiente en un mamífero que necesite de dicho tratamiento que comprende la administración al paciente de una cantidad terapéuticamente eficaz de un compuesto de la Reivindicación 1.

16. Un método para el tratamiento, control o prevención de la hiperglicemia en un paciente mamífero que necesite de dicho tratamiento, y que comprende la administración al mismo de una cantidad terapéuticamente eficaz de un compuesto de la Reivindicación 1.

17. Un método para el tratamiento, control o prevención de desordenes de lípidos, hiperlipidemia, o bajo HDL en un paciente mamífero que necesite de dicho tratamiento y que comprende la administración al mismo de una cantidad terapéuticamente eficaz de un compuesto de la Reivindicación 1.

18. Un método para el tratamiento, control o prevención de la obesidad en un paciente mamífero que necesite de dicho tratamiento y que comprende la administración al mismo de una cantidad terapéuticamente eficaz de un compuesto de la Reivindicación 1.

19. Un método para el tratamiento, control o prevención de la hipercolesterolemia en un paciente mamífero que necesite de dicho tratamiento y que comprende la administración al mismo de una cantidad terapéuticamente eficaz de un compuesto de la Reivindicación 1.

20. Un método para el tratamiento, control o prevención de la hipertrigliceridemia en un paciente mamífero que necesite de dicho tratamiento y que comprende la administración al mismo de una cantidad terapéuticamente eficaz de un compuesto de la Reivindicación 1.

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91

21. Un método para el tratamiento, control o prevención de la dislipidemia y/o bajo colesterol HDL en un paciente mamífero que necesite de dicho tratamiento y que comprende la administración al mismo de una cantidad terapéuticamente eficaz de un compuesto de la Reivindicación 1.

22. Un método para el tratamiento, control o prevención de la aterosclerosis en un paciente mamífero que necesite de dicho tratamiento y que comprende la administración al mismo de una cantidad terapéuticamente eficaz de un compuesto de la Reivindicación 1.

23. Un método para el tratamiento, control o prevención de una o varias enfermedades o trastornos o condiciones que se seleccionen a partir del grupo conformado por: (1) diabetes mellitus no insulino dependiente (NIDDM), (2) hiperglicemia, (3) baja tolerancia a la glucosa, (4) resistencia a la insulina, (5) obesidad, (6) desordenes de lípidos, (7) dislipidemia, (8) hiperlipidemia, (9) hipertrigliceridemia, (10) hipercolesterolemia, (11) bajos niveles de HDL, (12) altos niveles de LDL, (13) aterosclerosis y sus secuelas, (14) restenosis vascular, (15) síndrome de intestino irritable, (16) enfermedad inflamatoria intestinal, incluyendo la enfermedad de Crohn y la colitis ulcerativa, (17) otras condiciones inflamatorias, (18) pancreatitis, (19) obesidad abdominal, (20) enfermedad neurodegenerativa, (21) retinopatía, (22) condiciones neoplásicas, (23) tumores de las células adiposas, (24) carcinoma de las células adiposas, tales como liposarcoma, (25) cáncer de próstata y otros cánceres, incluyendo el

92

gástrico, de seno, de vejiga y de colón, (26) angiogénesis, (27) enfermedad de Alzheimer, (28) psoriasis, (29) alta presión arterial, (30) Síndrome X, (31) hiperandrogenismo de ovario (síndrome de ovario poliquístico), y otros desordenes en los cuales la resistencia a la insulina es un componente, donde el método comprende la administración de una cantidad eficaz de un compuesto de la Reivindicación 1.

24. Un método para el tratamiento, control o prevención de una o varias enfermedades, trastornos o condiciones que se seleccionen a partir del grupo conformado por: (1) diabetes mellitus, especialmente la diabetes mellitus no insulino dependiente (NIDDM), (2) hiperglicemia, (3) baja tolerancia a la glucosa, (4) resistencia a la insulina, (5) obesidad, (6) desordenes de lípidos, (7) dislipidemia, (8) hiperlipidemia, (9) hipertrigliceridemia, (10) hipercolesterolemia, (11) bajos niveles de HDL, (12) altos niveles de LDL, (13) aterosclerosis y sus secuelas, (14) restenosis vascular, (15) síndrome de intestino irritable, (16) enfermedad inflamatoria intestinal, incluyendo la enfermedad de Crohn y la colitis ulcerativa, (17) otras condiciones inflamatorias, (18) pancreatitis, (19) obesidad abdominal, (20) enfermedad neurodegenerativa, (21) retinopatía, (22) condiciones neoplásicas, (23) tumores de las células adiposas, (24) carcinoma de las células adiposas, tales como liposarcoma, (25) cáncer de próstata y otros cánceres, incluyendo el gástrico, de seno, de vejiga y de colón, (26) angiogénesis, (27) enfermedad de Alzheimer, (28) psoriasis, (29) alta presión arterial, (30) Síndrome X, (31) hiperandrogenismo de ovario (síndrome de ovario poliquístico), y otros desordenes

82
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en los cuales la resistencia a la insulina es un componente, donde el método comprende la administración de una cantidad eficaz de un compuesto de la Reivindicación 1, y una cantidad eficaz de uno o varios compuestos que se seleccionan a partir del grupo conformado por:

(a) sensibilizadores de la insulina que incluyen (i) agonistas PPAR γ tales como los glitazonas (por ejemplo troglitazona, pioglitazona, englitazona, MCC-555, rosiglitazona, y similares), y compuestos divulgados en WO97/27857, 97/28137 y 97/27847; (ii) biguanidas tales como metformina y fenformina; (iii) inhibidores de la fosfatasa - IB (PTP-IB) de la tirosina protéinica, y (iv) inhibidores de la peptidasa IV (DP-IV) del dipeptidilo;

(b) insulina o mimetizados de esta,

(c) sulfonilureas tales como tolbutamida y glipizida, o materiales relacionados;

(d) inhibidores de α -glucosidasa (tales como acarbosa);

(e) agentes para bajar el colesterol como (i) inhibidores de la reductasa HMG-CoA (lovastatina, sinvastatina, pravastatina, fluvastatina, atorvastatina, rivastatina, itavastatina, ZD-4522 y otras estatinas), (ii) secuestrantes (colestiramina, colestipol, y derivados del dialquilaminoalquilo dextran de enlace cruzado), (iii) alcohol nicotinilo, ácido nicotínico o una de sus sales, (iv) agonistas PPAR α tales como derivados del ácido fenofíbrico (genfibrozil, clofibrato, fenofibrato y benzafibrato), (v) agonistas duales PPAR α/γ , tales como KRP-297, (vi)

94

inhibidores de la absorción del colesterol, tales como el beta-sitosterol, (vii) acil CoA: inhibidores de la aciltransferasa de colesterol, tales como avasimibe, y (viii) anti-oxidantes, tales como probucol;

(f) agonistas PPAR δ tales como los descritos en WO97/28149;

(g) compuestos anti-obesidad tales como fenfluramina, dexfenfluramina, fentiramina, sulbitramina, orlistat, inhibidores del neuropéptido Y5, y agonistas del receptor adrenérgico β_3 ;

(h) un inhibidor del transportador del ácido biliar; y

(i) agentes diseñados para el uso de condiciones inflamatorias tales como aspirina, medicamentos anti-inflamatorios no esteroides, glucocorticoides, azulfidina, e inhibidores selectivos de la ciclo-oxigenasa 2.

25. Un método para el tratamiento, control o prevención de una o más condiciones seleccionadas a partir de la hipercolesterolemia, aterosclerosis, bajos niveles de HDL, altos niveles de LDL, hiperlipidemia, hipertrigliceridemia, y dislipidemia, donde el método comprende la administración a un paciente mamífero que requiera de dicho tratamiento de una cantidad terapéuticamente eficaz de un agonista doble PPAR α/γ .

26. El método descrito en la Reivindicación 25, donde el agonista doble PPAR α/γ se administra con un inhibidor de la reductasa HMG-CoA.

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27. El método según se describió en la Reivindicación 26, donde el inhibidor de la reductasa HMG-CoA es una estatina.

28. El método descrito en la Reivindicación 27, donde la estatina se selecciona a partir del grupo conformado por lovastatina, sinvastatina, pravastatina, fluvastatina, atorvastatina, itavastatina, ZD-4522 y rivastatina.

29. Un método para el tratamiento, control o prevención de una o más condiciones seleccionadas a partir de condiciones inflamatorias, enfermedad intestinal inflamatoria, enfermedad de Crohn y colitis ulcerática, donde el método comprende la administración a un paciente mamífero que lo requiera de una cantidad terapéuticamente eficaz de un agonista PPAR.

30. El método descrito en la Reivindicación 29, donde el mencionado agonista PPAR es un agonista doble PPAR α/γ .

31. El método según se describió en la Reivindicación 30, donde el agonista doble PPAR α/γ se administra con un inhibidor de la reductasa HMG-CoA.

32. El método según se describió en la Reivindicación 31, donde el agonista doble PPAR α/γ es un compuesto de acuerdo con la Reivindicación 1 y el inhibidor de la reductasa HMG-CoA es una estatina que se selecciona a partir del grupo conformado por lovastatina, sinvastatina, pravastatina, fluvastatina, atorvastatina, itavastatina, ZD-

4522 y rivastatina.

33. Un método para el tratamiento, prevención o control de la aterosclerosis en un paciente mamífero que requiera de dicho tratamiento y que comprende la administración al mismo de una cantidad eficaz de un compuesto de la Reivindicación 1 y de una cantidad eficaz de un inhibidor de la reductasa HMG-CoA.

34. Una composición farmacéutica para el tratamiento, prevención o control de la aterosclerosis, que comprende: (1) un compuesto de acuerdo con la Reivindicación 1, (2) un inhibidor de la reductasa HMG-CoA y (3) un portador farmacéuticamente aceptable.

35. Una composición farmacéutica que comprende (i) un compuesto de acuerdo con la Reivindicación 1, (2) uno o más compuestos seleccionados a partir del grupo conformado por:

(a) sensibilizadores de la insulina que incluyen (i) agonistas PPAR γ tales como los glitazonas (por ejemplo troglitazona, pioglitazona, englitazona, MCC-555, rosiglitazona, y similares), y compuestos divulgados en WO97/27857, 97/28137 y 97/27847; (ii) biguanidas tales como metformina y fenformina; (iii) inhibidores de la fosfatasa - IB (PTP-IB) de la tirosina protéinica, y (iv) inhibidores de la peptidasa IV (DP-IV) del dipeptidilo;

(b) insulina o mimetizados de esta,

(c) sulfonilureas tales como tolbutamida y glipizida, o

97

materiales relacionados;

(d) inhibidores de α -glucosidasa (tales como acarbosa);

(e) agentes para bajar el colesterol como (i) inhibidores de la reductasa HMG-CoA (lovastatina, sinvastatina, pravastatina, fluvastatina, atorvastatina, rivastatina, itavastatina, ZD-4522 y otras estatinas), (ii) secuestrantes (colestiramina, colestipol, y derivados del dialquilaminoalquilo dextran de enlace cruzado), (iii) alcohol nicotinilo, ácido nicotínico o una de sus sales, (iv) agonistas PPAR α tales como derivados del ácido fenofibrico (genfibrozil, clofibrato, fenofibrato y benzafibrato), (v) agonistas duales PPAR α/γ , tales como KRP-297, (vi) inhibidores de la absorción del colesterol, tales como el beta-sitosterol, (vii) acil CoA: inhibidores de la aciltransferasa de colesterol, tales como avasimibe, y (viii) anti-oxidantes, tales como probucol;

(f) agonistas PPAR δ tales como los descritos en WO97/28149;

(g) compuestos anti-obesidad tales como fenfluramina, dexfenfluramina, fentiramina, sulbitramina, orlistat, inhibidores del neuropéptido Y5, y agonistas del receptor adrenérgico β_3 ;

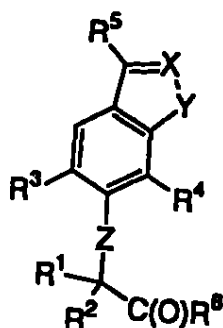
(h) un inhibidor del transportador del ácido biliar; y

(i) agentes diseñados para el uso de condiciones inflamatorias tales como aspirina, medicamentos anti-inflamatorios no esteroides, glucocorticoides, azulfidina, e inhibidores selectivos de la ciclo-oxigenasa 2; y

98

(3) un portador farmacéuticamente aceptable.

36. Un compuesto que tiene la formula Ia,



Ia

y sus sales farmacéuticamente aceptables, donde

R¹ y R² son cada uno de ellos y de manera independiente seleccionados a partir del grupo conformado por H, F, alquilo C₁₋₈, alquenilo C₂₋₈, y alquinilo C₂₋₈, donde los mencionados alquilo, alquenilo y alquinilo pueden ser lineales o bifurcados y sustituidos opcionalmente por 1-3 átomos de halógeno; u opcionalmente R¹ y R² conjuntamente forman un cicloalquilo C₃₋₈;

R³ y R⁴ se seleccionan cada uno de ellos y de manera independiente del grupo conformado por alquilo C₁₋₈, alquenilo C₂₋₈, alquinilo C₂₋₈, y cloro, con la condición de que R³ y R⁴ no sean ambos cloro, donde los mencionados grupos alquilo, alquenilo, y alquinilo pueden ser lineales o bifurcados, sustituyéndose opcionalmente por 1-5 átomos de flúor;

X es N o CR;

Y es O, S, o NR;

Z es O o S;

Cada R se selecciona independientemente del grupo conformado por H, alquilo C₁-s, alquenilo C₂-s, y alquinilo C₂-s, donde los mencionados alquilo, alquenilo y alquinilo pueden ser lineales o bifurcados y opcionalmente sustituidos por 1-5 átomos de flúor y/o un -OalquiloC₁-s, donde el mencionado -OalquiloC₁-s es sustituido opcionalmente por 1-7 átomos de flúor; y

R^s se selecciona a partir del grupo conformado por H, alquilo C₁-s, alquenilo C₂-s, alquinilo C₂-s, Arilo C₆-10, -OalquiloC₁-s, -OalqueniloC₂-s, -OalquiniloC₂-s, -OAriloC₆-10, Cicloalquilo C₃-s, Heterocíclico de 5-6 miembros, Heteroarilo de 5-6 miembros, -OCicloalquilo C₃-s, -O Heterocíclico de 5-6 miembros, -O Heteroarilo de 5-6 miembros, y el grupo alquilo C₁-4 que comprende en la posición "a" la interrupción de la cadena o al final de ésta un grupo que se selecciona a partir de Arilo C₆-10, Cicloalquilo C₃-s, Heterocíclico de 5-6 miembros, y Heteroarilo de 5-6 miembros, donde cada uno de los mencionados alquilo, alquenilo, alquinilo, -Oalquilo, -Oalquenilo, y -Oalquinilo, se sustituye opcionalmente por 1-5 átomos de flúor y/o un grupo -OCH₃ o -OCF₃, y cada uno de los mencionados grupos Arilo, Cicloalquilo, Heteroarilo, Heterocíclico, -OArilo, -OCicloalquilo, -OHeteroarilo, y -OHeterocíclico, se sustituye opcionalmente por 1-7 átomos de halógeno y/o un grupo -OCH₃ o -OCF₃;

100

R⁶ se selecciona a partir del grupo conformado por -OR⁷, -OCH₂OR⁷, -OCH(CH₃)OR⁷, -OCH₂OC(O)R⁷, -OCH(CH₃)OC(O)R⁷, -OCH₂OC(O)OR⁷, -OCH(CH₃)OC(O)OR⁷, -NR⁸R⁸, y -ONR⁸R⁸;

Cada R⁷ se selecciona independientemente a partir del alquilo C₁₋₆ sustituido opcionalmente por uno o dos grupos que se seleccionan a partir de -CO₂H, -CONH₂, -NH₂, -OH, -OAc, NHAc, y fenilo; y

Cada R⁸ se selecciona independientemente a partir de H y R⁷.

La anterior es Traducción Oficial de un documento presentado originalmente en inglés. Esta traducción fue realizada por GABRIEL RUEDA CHADID (Traductor Oficial). Resolución 5996 del Minjusticia, por lo cual estampo mi Sello y Firmo.

Bogotá D.C., Febrero 14 del 2001.

GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV. 29-00
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United States Patent and Trademark Office

November 17, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/183,593

FILING DATE: February 18, 2000

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS



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PROVISIONAL APPLICATION FOR PATENT COVER SHEET A/PROV

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c)

DOCKET NUMBER 20630PV

INVENTOR(S)

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☐ Additional inventors are being named on the separately numbered sheets attached hereto

TITLE OF THE INVENTION (250 characters max)

HYDROXYACETIC ACIDS FOR DIABETES AND LIPID DISORDERS

CORRESPONDENCE ADDRESS

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COUNTRY

U.S.A.

ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification Number of Pages 49☐ Drawing(s) Number of Sheets☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)

☐ A check or money order is enclosed to cover the filing fees☒ The Commissioner is hereby authorized to charge filing fees or credit to Deposit Account Number:

13-2755

FILING FEE
AMOUNT (\$)

\$150.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☐ No.☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE



Date

2/18/2000

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EXPRESS MAIL CERTIFICATE

DATE OF DEPOSIT February 18, 2000

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I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS EXPRESS MAIL "POST OFFICE TO ADDRESSEE" ON THE ABOVE DATE IN AN ENVELOPE ADDRESSED TO ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20531.

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TITLE OF THE INVENTION

ARYLOXYACETIC ACIDS FOR DIABETES AND LIPID DISORDERS

FIELD OF THE INVENTION

5 The instant invention is concerned with aryloxyacetic acids and pharmaceutically acceptable salts and prodrugs thereof which are useful as therapeutic compounds, particularly in the treatment of Type 2 diabetes mellitus, often referred to as non-insulin dependent diabetes (NIDDM), of conditions that are often associated with this disease, and of lipid disorders.

10

BACKGROUND OF THE INVENTION

Diabetes refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose or hyperglycemia in the fasting state or after administration of glucose during an oral glucose tolerance test.

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Persistent or uncontrolled hyperglycemia is associated with increased and premature morbidity and mortality. Often abnormal glucose homeostasis is associated both directly and indirectly with alterations of the lipid, lipoprotein and apolipoprotein metabolism and other metabolic and hemodynamic disease. Therefore patients with Type 2 diabetes mellitus are at especially increased risk of macrovascular and

20 microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therefore, therapeutical control of glucose homeostasis, lipid metabolism and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

20

There are two generally recognized forms of diabetes. In type 1

25 diabetes, or insulin-dependent diabetes mellitus (IDDM), patients produce little or no insulin, the hormone which regulates glucose utilization. In type 2 diabetes, or noninsulin dependent diabetes mellitus (NIDDM), patients often have plasma insulin levels that are the same or even elevated compared to nondiabetic subjects; however, these patients have developed a resistance to the insulin stimulating effect on glucose and lipid metabolism in the main insulin-sensitive tissues, which are muscle, liver and

30 adipose tissues, and the plasma insulin levels, while elevated, are insufficient to overcome the pronounced insulin resistance.

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Insulin resistance is not primarily due to a diminished number of insulin receptors but to a post-insulin receptor binding defect that is not yet

35 understood. This resistance to insulin responsiveness results in insufficient insulin

activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in the liver.

5 The available treatments for type 2 diabetes, which have not changed substantially in many years, have recognized limitations. While physical exercise and reductions in dietary intake of calories will dramatically improve the diabetic condition, compliance with this treatment is very poor because of well-entrenched sedentary lifestyles and excess food consumption, especially of foods containing high amounts of saturated fat. Increasing the plasma level of insulin by administration of
10 sulfonylureas (e.g. tolbutamide and glipizide), which stimulate the pancreatic β -cells to secrete more insulin, and/or by injection of insulin after the response to sulfonylureas fails, will result in high enough insulin concentrations to stimulate the very insulin-resistant tissues. However, dangerously low levels of plasma glucose can result from these last two treatments, and increasing insulin resistance due to the even
15 higher plasma insulin levels can occur. The biguanides increase insulin sensitivity resulting in some correction of hyperglycemia. However, the two biguanides, phenformin and metformin, can induce lactic acidosis and nausea/diarrhea, respectively.

20 The glitazones (i.e. 5-benzylthiazolidine-2,4-diones) are a more recently described class of compounds with potential for a novel mode of action in ameliorating many symptoms of type 2 diabetes. These agents substantially increase insulin sensitivity in muscle, liver and adipose tissue in several animal models of type 2 diabetes resulting in partial or complete correction of the elevated plasma levels of glucose without occurrence of hypoglycemia.

25 Disorders of lipid metabolism or dyslipidemias include various conditions characterized by abnormal concentrations of one or more lipids (i.e. cholesterol and triglycerides), and/or apolipoproteins (i.e., apolipoproteins A, B, C and E), and/or lipoproteins (i.e., the macromolecular complexes formed by the lipid and the apolipoprotein that allow lipids to circulate in blood, such as LDL, VLDL and
30 IDL). Cholesterol is mostly carried in Low Density Lipoproteins (LDL), and this component is commonly known as the "bad" cholesterol because it has been shown that elevations in LDL-cholesterol correlate closely to the risk of coronary heart disease. A smaller component of cholesterol is carried in the High Density Lipoproteins and is commonly known as the "good" cholesterol. In fact, it is known
35 that the primary function of HDL is to accept cholesterol deposited in the arterial wall

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and to transport it back to the liver for disposal through the intestine. Although it is desirable to lower elevated levels of LDL cholesterol, it is also desirable to increase levels of HDL cholesterol. Generally, it has been found that increased levels of HDL are associated with lower risk for coronary heart disease (CHD). See, for example,
 5 Gordon, et al., *Am. J. Med.*, 62, 707-714 (1977); Stampfer, et al., *N. England J. Med.*, 325, 373-381 (1991); and Kannel, et al., *Ann. Internal Med.*, 90, 85-91 (1979). An example of an HDL raising agent is nicotinic acid, a drug with limited utility because doses that achieve HDL raising are associated with undesirable effects, such as flushing.

10 Dyslipidemias were originally classified by Fredrickson according to the combination of alterations mentioned above. The Fredrickson classification includes 6 phenotypes (i.e., I, IIa, IIb, III, IV and V) with the most common being the isolated hypercholesterolemia (or type IIa) which is usually accompanied by elevated concentrations of total and LDL cholesterol. The initial treatment for
 15 hypercholesterolemia is often to modify the diet to one low in fat and cholesterol, coupled with appropriate physical exercise, followed by drug therapy when LDL-lowering goals are not met by diet and exercise alone

 A second common form of dyslipidemia is the mixed or combined hyperlipidemia or type IIb and III of the Fredrickson classification. This dyslipidemia
 20 is often prevalent in patients with type 2 diabetes, obesity and the metabolic syndrome. In this dyslipidemia there are modest elevations of LDL-cholesterol, accompanied by more pronounced elevations of small dense LDL-cholesterol particles, VLDL and/or IDL (i.e., triglyceride rich lipoproteins), and total triglycerides. In addition, concentrations of HDL are often low.

25 Peroxisome proliferators are a structurally diverse group of compounds that when administered to rodents elicit dramatic increases in the size and number of hepatic and renal peroxisomes, as well as concomitant increases in the capacity of peroxisomes to metabolize fatty acids via increased expression of the enzymes of the beta-oxidation cycle. Compounds of this group include but are not limited to the
 30 fibrate class of lipid modulating drugs, herbicides and phthalate plasticizers. Peroxisome proliferation is also triggered by dietary or physiological factors such as a high-fat diet and cold acclimatization.

 Three sub-types of peroxisome proliferator activated receptor (PPAR) have been discovered and described; they are peroxisome proliferator activated
 35 receptor alpha (PPAR α), peroxisome proliferator activated receptor gamma

(PPAR γ) and peroxisome proliferator activated receptor delta (PPAR δ). Identification of PPAR α , a member of the nuclear hormone receptor superfamily activated by peroxisome proliferators, has facilitated analysis of the mechanism by which peroxisome proliferators exert their pleiotropic effects. PPAR α is activated by a number of medium and long-chain fatty acids, and it is involved in stimulating β -oxidation of fatty acids. PPAR α is also associated with the activity of fibrates and fatty acids in rodents and humans. Fibrate acid derivatives such as clofibrate, fenofibrate, benzaifibrate, ciprofibrate, beclofibrate and etofibrate, as well as gemfibrozil, each of which are PPAR α ligands and/or activators, produce a substantial reduction in plasma triglycerides as well as some increase in HDL. The effects on LDL cholesterol are inconsistent and might depend upon the compound and/or the dyslipidemic phenotype. For these reasons, this class of compounds has been primarily used to treat hypertriglyceridemia (i.e., Fredrickson Type IV and V) and/or mixed hyperlipidemia.

The PPAR γ receptor subtypes are involved in activating the program of adipocyte differentiation and are not involved in stimulating peroxisome proliferation in the liver. There are two known protein isoforms of PPAR γ : PPAR γ 1 and PPAR γ 2 which differ only in that PPAR γ 2 contains an additional 28 amino acids present at the amino terminus. The DNA sequences for the human isotypes are described in Elbrecht, et al., BBRC 224:431-437 (1996). In mice, PPAR γ 2 is expressed specifically in fat cells. Tontonoz *et al.*, *Cell* 79: 1147-1156 (1994) provide evidence to show that one physiological role of PPAR γ 2 is to induce adipocyte differentiation. As with other members of the nuclear hormone receptor superfamily, PPAR γ 2 regulates the expression of genes through interaction with other proteins and binding to hormone response elements, for example in the 5' flanking regions of responsive genes. An example of a PPAR γ 2 responsive gene is the tissue-specific adipocyte P2 gene. Although peroxisome proliferators, including the fibrates and fatty acids, activate the transcriptional activity of PPAR's, only prostaglandin J₂ derivatives have been identified as potential natural ligands of the PPAR γ subtype, which also binds thiazolidinedione antidiabetic agents with high affinity.

The human nuclear receptor gene PPAR δ (hPPAR δ) has been cloned from a human osteosarcoma cell cDNA library and is fully described in A. Schmidt et al., *Molecular Endocrinology*, 6:1634-1641 (1992). It should be noted that PPAR δ is

also referred to in the literature as PPAR β and as NUC1, and each of these names refers to the same receptor; in Schmidt *et al.* the receptor is referred to as NUC1.

In WO96/01430, a human PPAR subtype, hNUC1B, is disclosed. The amino acid sequence of hNUC1B differs from human PPAR δ (referred to therein as hNUC1) by one amino acid, i.e., alanine at position 292. Based on in vivo experiments described therein, the authors suggest that hNUC1B protein represses hPPAR α and thyroid hormone receptor protein activity.

It has been disclosed in WO97/28149 that agonists of PPAR δ are useful in raising HDL plasma levels. WO97/27857, 97/28115, 97/28137 and 97/27847 disclose compounds that are useful as antidiabetic, antiobesity, anti-atherosclerosis and antihyperlipidemic agents, and which may exert their effect through activation of PPARs.

It is generally believed that glitazones exert their effects by binding to the peroxisome proliferator activated receptor (PPAR) family of receptors, controlling certain transcription elements having to do with the biological entities listed above. See Hulin *et al.*, Current Pharm. Design (1996) 2, 85-102.

A number of glitazones that are PPAR agonists have been approved for use in the treatment of diabetes. These include troglitazone, rosiglitazone and pioglitazone, all of which are primarily or exclusively PPAR γ agonists. Many of the newer PPAR agonists that are currently under development or are in clinical trials have dual PPAR α and γ activity. These are expected to improve both insulin sensitivity and the lipid profile in patients having NIDDM.

Although glitazones are beneficial in the treatment of NIDDM, there have been some serious adverse events associated with the use of the compounds. The most serious of these has been liver toxicity, which has resulted in a number of deaths. The most serious problems have occurred using troglitazone. Because of the problems that have occurred with the glitazones, researchers in a number of laboratories have been investigating classes of PPAR agonists that are not glitazones and do not contain 1,3-thiazolidinedione moieties.

Compounds that are not glitazones but are agonists of PPAR sub-types are expected to be useful in the treatment of diabetes and associated conditions. PPAR α agonists should improve the lipid profile and alleviate dyslipidemias by reducing elevated LDL levels and elevated triglyceride levels and/or increasing HDL

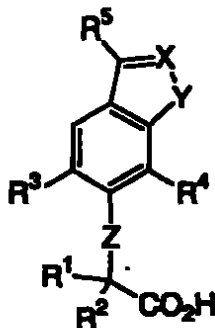
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levels. PPAR γ agonists should improve insulin sensitivity, reducing the need for insulin injections in patients with NIDDM. The role of PPAR δ is less well defined.

SUMMARY OF THE INVENTION

The class of compounds described herein is a new class of PPAR agonists that do not contain a 1,3-thiazolidinedione moiety and therefore are not glitazones. The class of compounds includes compounds that are primarily PPAR α agonists and compounds that are mixed PPAR α/γ agonists. These compounds are useful in the treatment, control and/or prevention of diabetes, hyperglycemia, mixed or diabetic dyslipidemia, and other lipid disorders (including isolated hypercholesterolemia as manifested by elevations in LDL-C and/or non-HDL-C and/or hyperapoproteinemia, hypertriglyceridemia and/or increase in triglyceride-rich-lipoproteins, or low HDL cholesterol concentrations), atherosclerosis, obesity, vascular restenosis, inflammatory conditions, neoplastic conditions, and other PPAR α and/or γ mediated diseases, disorders and conditions.

The present invention provides compounds having the structure of Formula I, including pharmaceutically acceptable salts and prodrugs of these compounds:



I

In the compounds of Formula I:

R^1 and R^2 are each independently selected from the group consisting of H, F, C₁₋₅ alkyl, C₂₋₅ alkenyl, and C₂₋₅ alkynyl, wherein said alkyl, alkenyl, and alkynyl may be linear or branched and are optionally substituted with 1-3 halogen atoms; or optionally R^1 and R^2 together form a C₃₋₆ cycloalkyl:

5

R^3 and R^4 are each independently selected from the group consisting of C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and chlorine, provided that R^3 and R^4 are not both chlorine, wherein said alkyl, alkenyl, and alkynyl groups may be linear or branched and are optionally substituted with 1-5 fluorine atoms;

10

X is N or CR;

Y is O, S, or NR;

15

Z is O or S;

Each R group is selected from the group consisting of H, C₁₋₅ alkyl, C₂₋₅ alkenyl, and C₂₋₅ alkynyl, wherein said alkyl, alkenyl, and alkynyl may be linear or branched and are optionally substituted with 1-5 fluorine atoms and/or one -OC₁₋₃ alkyl, said -OC₁₋₃ alkyl being optionally substituted with 1-7 fluorine atoms; and

20

R^5 is selected from the group consisting of H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ Aryl, -OC₁₋₆ alkyl, -OC₂₋₆ alkenyl, -OC₂₋₆ alkynyl, -OC₆₋₁₀ Aryl, C₃₋₆ Cycloalkyl, 5-6-membered Heterocyclyl, 5-6-membered Heteroaryl, -OC₃₋₆ Cycloalkyl, -O 5-6-membered Heterocyclyl, -O 5-6 membered Heteroaryl, and a C₁₋₄ alkyl group which comprises at a position interrupting the chain or at the end of the chain a group selected from C₆₋₁₀ Aryl, C₃₋₆ Cycloalkyl, 5-6-membered Heterocyclyl, and 5-6-membered Heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, -Oalkyl, -Oalkenyl, and -Oalkynyl is optionally substituted with 1-5 fluorine atoms and/or one -OCH₃ or -OCF₃ group, and each of said Aryl, Cycloalkyl, Heteroaryl, Heterocyclyl, -OAryl, -OCycloalkyl, -OHeteroaryl, and -OHeterocyclyl groups is optionally substituted with 1-7 halogen atoms and/or one -OCH₃ or -OCF₃ group.

25

30

These compounds are effective in lowering glucose, lipids, and insulin in diabetic animals. The compounds are expected to be efficacious in the treatment, control and/or prevention of non-insulin dependent diabetes mellitus (NIDDM) in humans and in the treatment, control, and/or prevention of conditions associated with NIDDM, including hyperlipidemia, dyslipidemia, obesity, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, vascular restenosis, inflammatory conditions, neoplastic conditions, and other PPAR α and/or γ mediated diseases, disorders and conditions.

DETAILED DESCRIPTION OF THE INVENTION

The invention has numerous embodiments. Several subsets of compounds having different heterocyclic rings are included, as follows:

Compounds of Formula I, in which X is N and Y is O;

Compounds of Formula I, in which X is N and Y is S;

Compounds of Formula I, in which X is N and Y is NR;

Compounds of Formula I, in which X is CR and Y is O;

Compounds of Formula I, in which X is CR and Y is S; and

Compounds of Formula I, in which X is CR and Y is NR.

In further subsets of the compounds of Formula I described above, in which the compounds of Formula I have different heterocycles fused to the aromatic ring, (i.e. different values of X and Y), R⁵ is selected from the group consisting of H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, OC₁₋₅ alkyl, OC₂₋₅ alkenyl, OC₂₋₅ alkynyl, and phenoxy; in these compounds, the alkyl, alkenyl, alkynyl, -Oalkyl, -Oalkenyl, and -Oalkynyl are optionally substituted with 1-5 fluorine atoms, and phenoxy is optionally substituted with 1-5 halogens.

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111

In a preferred subset of the compounds described immediately above, R^1 and R^2 are each H or C_{1-3} alkyl, and the number of carbon atoms in R^1 and R^2 together is 0-5;

5 R^3 and R^4 are each independently C_{1-5} alkyl, and in preferred embodiments at least one of R^3 and R^4 is C_{2-5} alkyl, and in more preferred embodiments, both R^3 and R^4 are C_{2-5} alkyl;

10 R^5 is selected from the group consisting of C_{1-5} alkyl and $-OC_{1-5}$ alkyl, where the alkyl and $-Oalkyl$ are optionally substituted with 1-5 fluorine atoms, and

Z is O.

15 In a highly preferred embodiment of the group of compounds above, R^5 is C_{1-3} alkyl, $-OC_{1-3}$ alkyl, CF_3 , C_2F_5 , $-OCF_3$ or $-OC_2F_5$; and R^3 and R^4 are each n-propyl.

Specific examples of compounds of this invention are provided as Examples 1-29.

20

The invention further includes pharmaceutical compositions comprising any of the compounds described above and a pharmaceutically acceptable carrier.

25 The compounds as defined above are useful in the following methods of treating, controlling, and preventing diseases, as well as other diseases not listed below:

30 (1) a method for treating, controlling or preventing diabetes mellitus, and particularly non-insulin dependent diabetes mellitus, in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Formula I;

(2) a method for treating, controlling, or preventing hyperglycemia in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Formula I;

35 (3) a method for treating, controlling, or preventing lipid disorders, hyperlipidemia, or low HDL in a mammalian patient in need of such treatment which

0183593-021800

comprises administering to the patient a therapeutically effective amount of a compound of Formula I;

(4) a method for treating, controlling, or preventing obesity in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Formula I;

(5) a method for treating, controlling, or preventing hypercholesterolemia in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Formula I;

(6) a method for treating, controlling, or preventing hypertriglyceridemia in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Formula I;

(7) a method for treating, controlling, or preventing dyslipidemia, including low HDL cholesterol, in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Formula I;

(8) a method for treating, controlling, or preventing atherosclerosis in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Formula I. It is understood that the sequelae of atherosclerosis (angina, claudication, heart attack, stroke, etc.) are thereby treated.

Definitions

"Ac" is acetyl, which is $\text{CH}_3\text{C}(\text{O})-$.

"Alkyl", as well as other groups having the prefix "alk", such as alkoxy or alkanoyl, means carbon chains which may be linear or branched or combinations thereof, unless the carbon chain is defined otherwise. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like.

"Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

"Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

5 "Cycloalkyl" means mono- or bicyclic saturated carbocyclic rings, each having from 3 to 10 carbon atoms. The term also includes a monocyclic ring fused to an aryl group in which the point of attachment is on the non-aromatic portion. Examples of cycloalkyl include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

10 "Aryl" (and "arylene") means mono- or bicyclic aromatic rings, containing only carbon ring atoms. The term also includes an aryl group fused to a monocyclic cycloalkyl or monocyclic heterocyclic group in which the point(s) of attachment is on the aromatic portion. "Heterocyclyl," "Heterocycle," and "heterocyclic" means a fully or partially saturated monocyclic, bicyclic or tricyclic
15 ring containing at least one heteroatom selected from N, S and O, each of said rings having from 3 to 10 atoms. Examples of aryl include phenyl, naphthyl, indanyl, indenyl, and tetrahydronaphthyl. Examples of aryl fused to heterocyclic groups include 2,3-dihydrobenzofuranyl, benzopyranyl, 1,4-benzodioxanyl, and the like. Examples of heterocycles include tetrahydrofuran, piperazine, and morpholine.

20 "Heteroaryl" (and heteroarylene) means a mono-, bi- or tricyclic aromatic ring containing at least one ring heteroatom selected from N, O and S (including SO and SO₂), with each ring containing 5 to 6 atoms. Examples of heteroaryl include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl,
25 thienyl, pyrimidyl, pyridazinyl, pyrazinyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl (including S-oxide and dioxide), furo(2,3-b)pyridyl, quinolyl, indolyl, isoquinolyl, dibenzofuran and the like.

"Halogen" includes fluorine, chlorine, bromine and iodine.

30 The term "composition," as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types
35 of reactions or interactions of one or more of the ingredients. Accordingly, the

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pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

5 Optical Isomers - Diastereomers - Geometric Isomers - Tautomers

Compounds of Formula I may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of Formula I.

10 Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. Such an example may be a ketone and its enol form, known as keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of Formula I.

15 Compounds of the Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid or base as a resolving agent.

20 Alternatively, any enantiomer of a compound of the general Formula I or Ia may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

25

Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, 30 manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines

including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

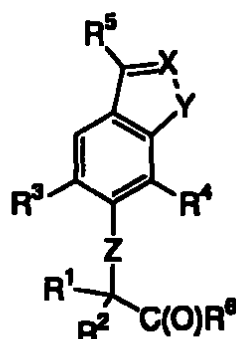
When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

20 Metabolites – Prodrugs

Metabolites of the compounds of this invention that are therapeutically active also are within the scope of the claimed parent compound. Prodrugs, which are compounds that are converted to the claimed compounds as they are being administered to a patient or after they have been administered to a patient, are also within the scope of the claimed active compound. A non-limiting example of a prodrug of the carboxylic acids of this invention would be an ester of the carboxylic acid group, for example a C₁ to C₆ ester, which may be linear or branched, or an ester which has functionality that makes it more easily hydrolyzed after administration to a patient.

30 Prodrugs of this class of compounds may be described as compounds having the Formula Ia:



Ia

wherein R^6 is a group that is easily removed under physiological conditions during or after administration to a mammalian patient to yield a compound having Formula I, or the carboxylate anion thereof (in solution), or a pharmaceutically acceptable salt thereof, where R^1 , R^2 , R^3 , R^4 , R^5 , X , Y , Z , and R are as defined above for compounds having Formula I.

Examples of prodrugs of Formula Ia include compounds in which R^6 is selected from the group consisting of $-OR^7$, $-OCH_2OR^7$, $-OCH(CH_3)OR^7$, $-OCH_2OC(O)R^7$, $-OCH(CH_3)OC(O)R^7$, $-OCH_2OC(O)OR^7$, $-OCH(CH_3)OC(O)OR^7$, $-NR^8R^8$, and $-ONR^8R^8$, where each R^7 is independently selected from C_{1-6} alkyl optionally substituted with one or two groups selected from $-CO_2H$, $-CONH_2$, $-NH_2$, $-OH$, $-OAc$, $NHAc$, and phenyl; and wherein each R^8 is independently selected from H and R^7 . Compounds having Formula Ia, where R^6 has the chemical structure described above, are described as prodrugs. However, regardless of whether they are active as prodrugs, yielding compounds or salts of Formula I, or whether they have a different means of exhibiting pharmaceutical activity, the compounds of Formula Ia are included in this invention. Such compounds are claimed herein, regardless of the mechanism leading to their activity.

The description of utility, pharmaceutical compositions, combination therapies, administration, dosage, and the like are all described in terms of compounds of Formula I. These descriptions of utility, etc. also apply to compounds of Formula Ia.

Utilities

Compounds of the present invention are potent agonists of various peroxisome proliferator activator receptor subtypes, particularly PPAR α and/or PPAR γ . Compounds of the present invention may be selective agonists of one receptor subtype, e.g. PPAR γ or PPAR α agonists, or they may be agonists of more than one receptor subtypes, e.g. dual PPAR α/γ agonists. Compounds of the present invention are useful in treating, controlling or preventing diseases, disorders or conditions, wherein the treatment is mediated by the activation of an individual PPAR subtype (α or γ), or a combination of PPAR subtypes (e.g. α/γ). Thus one aspect of the present invention provides a method for the treatment, control or prevention of such diseases, disorders, or conditions in a mammal which comprises administering to such mammal a therapeutically effective amount of a compound of Formula I. The diseases, disorders or conditions for which compounds of the present invention are useful in treating, controlling or preventing include, but are not limited to, (1) diabetes mellitus, and especially non-insulin dependent diabetes mellitus (NIDDM), (2) hyperglycemia, (3) low glucose tolerance, (4) insulin resistance, (5) obesity, (6) lipid disorders, (7) dyslipidemia, (8) hyperlipidemia, (9) hypertriglyceridemia, (10) hypercholesterolemia, (11) low HDL levels, (12) high LDL levels, (13) atherosclerosis and its sequelae, (14) vascular restenosis, (15) irritable bowel syndrome, (16) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (17) other inflammatory conditions, (18) pancreatitis, (19) abdominal obesity, (20) neurodegenerative disease, (21) retinopathy, (22) neoplastic conditions, (23) adipose cell tumors, (24) adipose cell carcinomas, such as liposarcoma, (25) prostate cancer and other cancers, including gastric, breast, bladder and colon cancers, (26) angiogenesis, (27) Alzheimer's disease, (28) psoriasis, (29) high blood pressure, (30) Syndrome X, (31) ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component.

Another aspect of the invention provides a method for the treatment, control, or prevention of hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia, and/or dyslipidemia, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of an agonist of PPAR α and/or PPAR γ or a PPAR α/γ dual agonist. The PPAR agonist may be used alone or advantageously may be administered with a cholesterol biosynthesis inhibitor, particularly an HMG-CoA reductase inhibitor such as lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin,

or ZD-4522. The PPAR agonist may also be used advantageously in combination with other lipid lowering drugs such as cholesterol absorption inhibitors (for example stanol esters, sterol glycosides such as tiqueside, and azetidinones such as ezetimibe), ACAT inhibitors (such as avasimibe), and with niacin, bile acid sequestrants, microsome triglyceride transport inhibitors, and bile acid reuptake inhibitors. These combination treatments may also be effective for the treatment, control or prevention of one or more related conditions selected from the group consisting of hypercholesterolemia, atherosclerosis, hyperlipidemia, hypertriglyceridemia, dyslipidemia, high LDL, and low HDL.

- Another aspect of the invention provides a method of treating inflammatory conditions, including inflammatory bowel disease, Crohn's disease, and ulcerative colitis by administering an effective amount of a PPAR agonist, which may be a PPAR α agonist, a PPAR γ agonist, or a PPAR α/γ dual agonist. Additional inflammatory diseases that may be treated with the instant invention include gout, rheumatoid arthritis, osteoarthritis, multiple sclerosis, asthma, ARDS, psoriasis, vasculitis, ischemia/reperfusion injury, frostbite, and related diseases.

Administration and Dose Ranges

- Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of Formula I are administered orally.

- The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

- When treating or preventing diabetes mellitus and/or hyperglycemia or hypertriglyceridemia or other diseases for which compounds of Formula I are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, preferably from about 1 milligrams to about 50 milligrams. In the

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119

case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

5 Pharmaceutical Compositions

Another aspect of the present invention provides pharmaceutical compositions which comprise a compound of Formula I and a pharmaceutically acceptable carrier. The pharmaceutical compositions of the present invention comprise a compound of Formula I or a pharmaceutically acceptable salt or prodrug thereof as an active ingredient, as well as a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical

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carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between
5 about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such
10 as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

15 Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

20 Compounds of formula I may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to
25 prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be
30 stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

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Combination Therapy

Compounds of Formula I may be used in combination with other drugs that may also be useful in the treatment, prevention, suppression or amelioration of the diseases or conditions for which compounds of Formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of Formula I is preferred. However, the combination therapy also includes therapies in which the compound of Formula I and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compound of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of Formula I.

Examples of other active ingredients that may be administered in combination with a compound of Formula I, and either administered separately or in the same pharmaceutical composition, include, but are not limited to:

- (a) insulin sensitizers including (i) PPAR γ agonists such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone, and the like), and compounds disclosed in WO97/27857, 97/28115, 97/28137 and 97/27847; (ii) biguanides such as metformin and phenformin; (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors, and (iv) dipeptidyl peptidase IV (DP-IV) inhibitors;
- (b) insulin or insulin mimetics;
- (c) sulfonylureas such as tolbutamide and glipizide, or related materials;
- (d) α -glucosidase inhibitors (such as acarbose);
- (e) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, ZD-4522 and other statins), (ii) sequestrants (cholestyramine, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) nicotinic alcohol, nicotinic acid or a salt thereof, (iv) PPAR α agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and benzafibrate), (v)

122

PPAR α/γ dual agonists, such as KRP-297, (vi) inhibitors of cholesterol absorption, such as for example beta-sitosterol, (vii) acyl CoA:cholesterol acyltransferase inhibitors, such as for example avasimibe, and (viii) anti-oxidants, such as probucol;

(f) PPAR δ agonists such as those disclosed in WO97/28149;

5 (g) antiobesity compounds such as fenfluramine, dexfenfluramine, phentiramine, sulbitramine, orlistat, neuropeptide Y5 inhibitors, and β_3 adrenergic receptor agonists;

(h) an ileal bile acid transporter inhibitor; and

(i) agents intended for use in inflammatory conditions such as aspirin,

10 non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, and cyclo-oxygenase 2 selective inhibitors.

The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds. Non-limiting examples include combinations of
15 compounds having Formula I with two or more active compounds selected from biguanides, sulfonylureas, HMG-CoA reductase inhibitors, other PPAR agonists, PTP-1B inhibitors, DP-IV inhibitors, and anti-obesity compounds.

BIOLOGICAL ASSAYS

20 A) PPAR Binding Assays

For preparation of recombinant human PPAR γ , PPAR δ , and PPAR α : Human PPAR γ , human PPAR δ and human PPAR α were expressed as glutathion fusion proteins in *E. coli*. The full length human cDNA for PPAR γ_2 was subcloned into the pGEX-2T expression vector (Pharmacia). The full length human cDNAs for
25 PPAR δ and PPAR α were subcloned into the pGEX-KT expression vector (Pharmacia). *E. coli* containing the respective plasmids were propagated, induced, and harvested by centrifugation. The resuspended pellet was broken in a French press and debris was removed by centrifugation at 12,000 X g. Recombinant human PPAR receptors were purified by affinity chromatography on glutathione sepharose. After
30 application to the column, and one wash, receptor was eluted with glutathione. Glycerol (10%) was added to stabilize the receptor and aliquots were stored at -80°C. For binding to PPAR γ , an aliquot of receptor was incubated in TEGM (10 mM Tris,

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pH 7.2, 1 mM EDTA, 10% glycerol, 7 μ L/100 mL β -mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreitol, 5 μ g/mL aprotinin, 2 μ g/mL leupeptin, 2 μ g/mL benzamidine and 0.5 mM PMSF) containing 0.1% non-fat dry milk and 10 nM [^{3} H] AD5075, (21 Ci/mmol), $\pm$ test compound as described in Berger et al (Novel peroxisome proliferator-activated receptor (PPAR γ) and PPAR δ ligands produce distinct biological effects. J. Biol. Chem. (1999), 274: 6718-6725. Assays were incubated for ~16 hr at 4°C in a final volume of 150 μ L. Unbound ligand was removed by incubation with 100 μ L dextran/gelatin-coated charcoal, on ice, for ~10 min. After centrifugation at 3000 rpm for 10 min at 4°C. 50 μ L of the supernatant fraction was counted in a Topcount.

For binding to PPAR δ , an aliquot of receptor was incubated in TEGM (10 mM Tris, pH 7.2, 1 mM EDTA, 10% glycerol, 7 μ L/100 mL β -mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreitol, 5 μ g/mL aprotinin, 2 μ g/mL leupeptin, 2 μ g/mL benzamide and 0.5 mM PMSF) containing 0.1% non-fat dry milk and 2.5 nM [^{3} H]L-783483, (17 Ci/mmol), $\pm$ test compound as described in Berger et al (Novel peroxisome proliferator-activated receptor (PPAR γ) and PPAR δ ligands produce distinct biological effects. 1999 J Biol Chem 274: 6718-6725). (L-783483 is 3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid, Ex. 20 in WO 97/28137). Assays were incubated for ~16 hr at 4°C in a final volume of 150 μ L. Unbound ligand was removed by incubation with 100 μ L dextran/gelatin-coated charcoal, on ice, for ~10 min. After centrifugation at 3000 rpm for 10 min at 4°C, 50 μ L of the supernatant fraction was counted in a Topcount.

For binding to PPAR α , an aliquot of receptor was incubated in TEGM (10 mM Tris, pH 7.2, 1 mM EDTA, 10% glycerol, 7 μ L/100 mL β -mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreitol, 5 μ g/mL aprotinin, 2 μ g/mL leupeptin, 2 μ g/mL benzamide and 0.5 mM PMSF) containing 0.1% non-fat dry milk and 5.0 nM [^{3} H]L-797773, (34 Ci/mmol), $\pm$ test compound. (L-797733 is (3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy))phenylacetic acid, Ex.62 in WO

97/28137). Assays were incubated for ~16 hr at 4°C in a final volume of 150 µL. Unbound ligand was removed by incubation with 100 µL dextran/gelatin-coated charcoal, on ice, for ~10 min. After centrifugation at 3000 rpm for 10 min at 4°C, 50 µL of the supernatant fraction was counted in a Topcount.

5

B). Gal-4 hPPAR Transactivation Assays

The chimeric receptor expression constructs, pcDNA3-hPPAR γ /GAL4, pcDNA3-hPPAR δ /GAL4, pcDNA3-hPPAR α /GAL4 were prepared by inserting the yeast GAL4 transcription factor DBD adjacent to the ligand binding domains (LBDs) of hPPAR γ , hPPAR δ , hPPAR α , respectively. The reporter construct, pUAS(5X)-tk-luc was generated by inserting 5 copies of the GAL4 response element upstream of the herpes virus minimal thymidine kinase promoter and the luciferase reporter gene. pCMV-lacZ contains the galactosidase Z gene under the regulation of the cytomegalovirus promoter. COS-1 cells were seeded at 12×10^3 cells/well in 96 well cell culture plates in high glucose Dulbecco's modified Eagle medium (DMEM) containing 10% charcoal stripped fetal calf serum (Gemini Bio-Products, Calabasas, CA), nonessential amino acids, 100 units/ml Penicillin G and 100 mg/ml Streptomycin sulfate at 37 °C in a humidified atmosphere of 10% CO₂. After 24 h, transfections were performed with Lipofectamine (GIBCO BRL, Gaithersburg, MD) according to the instructions of the manufacturer. Briefly, transfection mixes for each well contained 0.48 µl of Lipofectamine, 0.00075 µg of pcDNA3-PPAR/GAL4 expression vector, 0.045 µg of pUAS(5X)-tk-luc reporter vector and 0.0002 µg of pCMV-lacZ as an internal control for transactivation efficiency. Cells were incubated in the transfection mixture for 5 h at 37° C in an atmosphere of 10% CO₂. The cells were then incubated for ~48 h in fresh high glucose DMEM containing 5% charcoal stripped fetal calf serum, nonessential amino acids, 100 units/ml Penicillin G and 100 mg/ml Streptomycin sulfate $\pm$ increasing concentrations of test compound. Since the compounds were solubilized in DMSO, control cells were incubated with equivalent concentrations of DMSO; final DMSO concentrations were $\leq$ 0.1%, a concentration

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x29
n5

which was shown not to effect transactivation activity. Cell lysates were produced using Reporter Lysis Buffer (Promega, Madison, WI) according to the manufacturer's instructions. Luciferase activity in cell extracts was determined using Luciferase Assay Buffer (Promega, Madison, WI) in an ML3000 luminometer (Dynatech Laboratories, Chantilly, VA). β -galactosidase activity was determined using β -D-galactopyranoside (Calbiochem, San Diego, CA).

C. *In Vivo* Studies

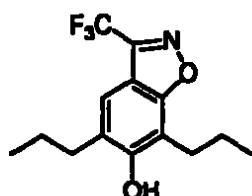
Male db/db mice (10-11 week old C57Bl/KfJ, Jackson Labs, Bar Harbor, ME) were housed 5/cage and allowed *ad lib.* access to ground Purina rodent chow and water. The animals, and their food, were weighed every 2 days and were dosed daily by gavage with vehicle (0.5% carboxymethylcellulose) $\pm$ test compound at the indicated dose. Drug suspensions were prepared daily. Plasma glucose, and triglyceride concentrations were determined from blood obtained by tail bleeds at 3-5 day intervals during the study period. Glucose, and triglyceride, determinations were performed on a Boehringer Mannheim Hitachi 911 automatic analyzer (Boehringer Mannheim, Indianapolis, IN) using heparinized plasma diluted 1:6 (v/v) with normal saline. Lean animals were age-matched heterozygous mice maintained in the same manner.

20

EXAMPLES

The following Examples are provided only to illustrate the invention, including methods of making the compounds of the invention, and are not to be construed as limiting the invention in any manner.

INTERMEDIATE 1



Step 1. Preparation of 1,3-diallyloxybenzene:

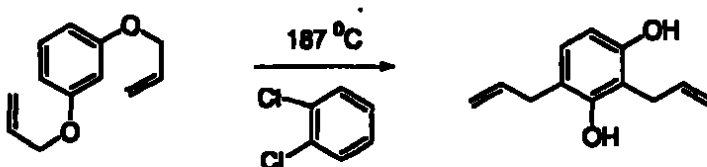


5

To a solution of resorcinol (1,200 g, 10.9 mmol) in DMF (10.89 L) was added K_2CO_3 (4,463 g). Allyl bromide (3,811 mL) was added slowly (keeping the temperature below 30 °C). The reaction mixture was stirred at ambient temperature overnight, poured into water (94 L), extracted with Et_2O (3 x 20L). Combined organic layers were washed with water (3 x 15 L) and brine (10 L), dried over $MgSO_4$, filtered through Na_2SO_4 , and evaporated in vacuo. The residue was pumped dry on high vacuum to give the crude product as a red/yellow oil, which was used in the next step without further purification. ^1H NMR ($CDCl_3$, 400 MHz) δ 4.5 (d, 4H), 5.27 (m, 2H), 5.42 (m, 2H), 6.05 (m, 2H), 6.5 (m, 3H), 7.16 (m, 1H).

15

Step 2. Preparation of 2,4-diallylresorcinol:



20

The crude starting material (2,278 g) was dissolved in 1,2-dichlorobenzene (11.4 L) in a 22 L 4-neck flask equipped with a mechanical stirrer, a thermocouple, a distillation condenser and a nitrogen inlet. A portion of the solvent (1.7 L) was distilled off at 187 °C before the distillation condenser was switched to a reflux condenser. The reaction was refluxed at 187 °C overnight. Ice-water (4 L) was

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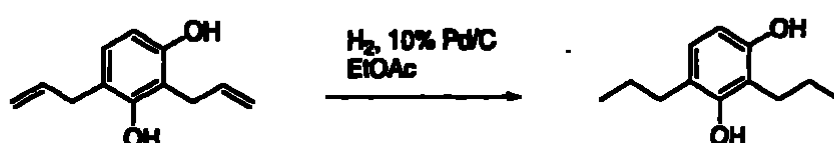
127

added, followed by NaOH (320 g). The mixture was poured into hexanes (12 L) and layers were separated. The organic layer was extracted with aqueous NaOH (2 N, 2 x 4 L). The combined aqueous layers were acidified with concentrated HCl (ice was added to maintain the temperature below 30 °C), then extracted with Et₂O (3 x 4 L).

5 The combined organic layers were dried over MgSO₄, filtered through Na₂SO₄, and evaporated in vacuo. Purification by chromatography (12 kg silica gel packed in hexanes, eluted with 10% EtOAc/hexanes) to give the desired product. ¹H NMR (CDCl₃, 400 MHz) δ 3.31 (m, 2H), 3.48 (m, 2H), 5.2 (m, 4H), 6.0 (m, 2H), 6.40 (d, 1H), 6.85 (d, 1H).

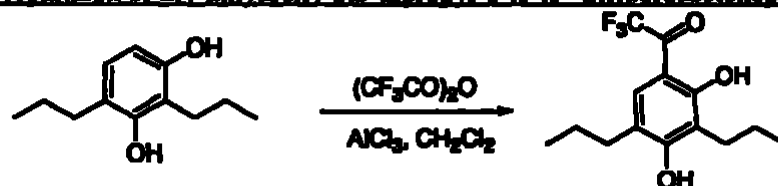
10

Step 3. Preparation of 2,4-dipropylresorcinol:



15 Starting material (1237.2 g, 6.5 mmol) was split into two runs. To each solution of the bis-allyl starting material (618.6 g) in ethyl acetate (2,780 mL) was added 10% Pd/C (46 g). Hydrogenation was carried out at rt under 40 psi hydrogen atmosphere for 1.5 h. The reaction was filtered through super cell, and the solvent was evaporated in vacuo. The combined crude products from the two runs were slurried in
20 hexanes, filtered, and dried to give the product. ¹H NMR (CDCl₃, 400 MHz) δ 1.00 (m, overlapping signals, 6H), 1.6 (m, overlapping signals, 4H), 2.48 (t, 2H), 2.60 (t, 2H), 4.56 (s, 1H), 4.70 (s, 1H), 6.31 (d, 1H), 6.80 (d, 1H).

Step 4. Preparation of 2,4-dihydroxy-3,5-dipropyl-1',1',1'-trifluoroacetonephenone:



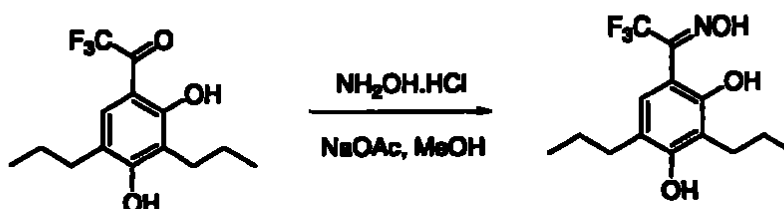
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To a solution of the starting material (785.7 g, 4.04 mmol) in CH₂Cl₂ (20,600 mL) was added AlCl₃ (1,763 g). Trifluoroacetic anhydride (814 mL) was added slowly at 0 °C. The reaction mixture was stirred overnight at rt, poured into ice-water.

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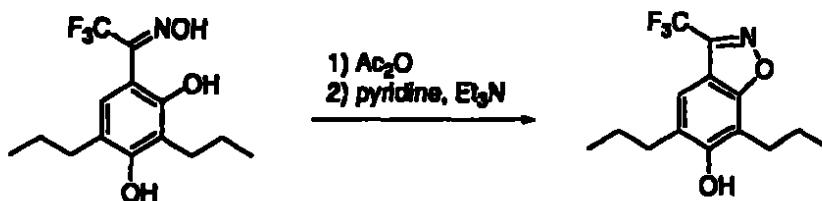
extracted with CH_2Cl_2 (3 x). The combined organic layers were washed with sat. NaHCO_3 and brine, dried over MgSO_4 , filtered through Na_2SO_4 , and evaporated in vacuo. Purification by chromatography (10 kg silica gel, packed in hexanes, eluted with 5% EtOAc/hexanes) to give the desired product as a yellow solid. ^1H NMR (CDCl_3 , 400 MHz) δ 1.00 (m, overlapping signals, 6H), 1.60 (m, overlapping signals, 4H), 2.55 (t, $J = 7.4$ Hz, 2H), 2.66 (t, $J = 7.4$ Hz, 2H), 5.65 (s, 1H), 7.45 (s, 1H); MS (ESI) 291 ($M + 1$).

Step 5. Preparation of 2,4-dihydroxy-3,5-dipropyl-1',1',1'-trifluoroacetonephenone oxime:



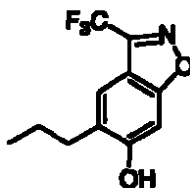
To a mixture of NaOAc (2,677 g, 32.5 mol) and hydroxylamine hydrochloride (2,000 g, 28.8 mol) in methanol (1 L) was added a solution of the starting phenol (1,139.8 g, 3.93 mol) in methanol (26 L). The yellow suspension was refluxed for 18 h. TLC showed significant amount of starting material remained. Additional hydroxylamine hydrochloride (1,000 g), NaOAc (1,338 g) and methanol (4 L) were added. The reaction mixture was refluxed overnight. TLC indicated the complete consumption of the starting material. The reaction was poured into ice-water (32 L), extracted with EtOAc (2 x 16 L). The combined organic layers were washed with brine, dried, and evaporated in vacuo. Chromatography (10 kg silica gel, 15% EtOAc/hexanes) gave the desired product as yellow solid. ^1H NMR (CDCl_3 , 400 MHz) δ 0.98 (m, overlapping signals, 6H), 1.60 (m, overlapping signals, 4H), 2.50 (t, 2H), 2.68 (t, 2H), 5.00 (s, broad, 1H), 5.80 (s, broad, 1H), 6.92 (s, 1H).

Step 6. Preparation of 5,7-dipropyl-6-hydroxy-3-trifluoromethyl-1,2-benzisoxazole:



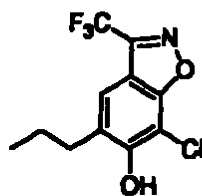
A solution of the starting oxime (600 g) in Ac_2O (3 L) was stirred at rt overnight. The solvent was removed in vacuo. The residue was coevaporated with toluene (4 x) to give the crude 2,4-dihydroxy-3,5-dipropyl-1,1,1'-trifluoroacetonephenone O-acetyl oxime. This crude product was dissolved in pyridine (6 L) and Et_3N (684 mL). The reaction was refluxed (112 °C) for 3 h, and allowed to cool overnight. The solvent was evaporated in vacuo. The residue was coevaporated with toluene (2 x), then partitioned between EtOAc and 1 N HCl. The organic layer was washed with 1 N HCl and brine, dried, filtered, and concentrated in vacuo to give a black oil. Purification by flash chromatography (10 kg silica gel, 5% EtOAc/hexanes) gave the desired product. ^1H NMR (CDCl_3 , 400 MHz) δ 1.00 (m, overlapping signals, 6H), 1.70 (m, overlapping signals, 4H), 2.68 (t, 2H), 2.90 (t, 2H), 5.21 (s, 1H), 7.33 (s, 1H); MS (ESI) 288.3 (M +1).

INTERMEDIATE 2



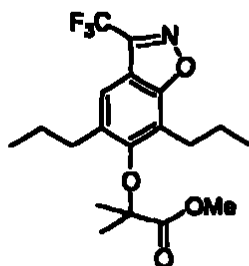
Similarly prepared as Intermediate 1 using 6-propylresorcinol. ^1H NMR (CDCl_3 , 400 MHz) δ 1.03 (t, 3H), 1.71 (m, 2H), 2.72 (t, 2H), 5.5 (s, broad, 1H), 7.06 (s, 1H), 7.51 (s, 1H).

INTERMEDIATE 3

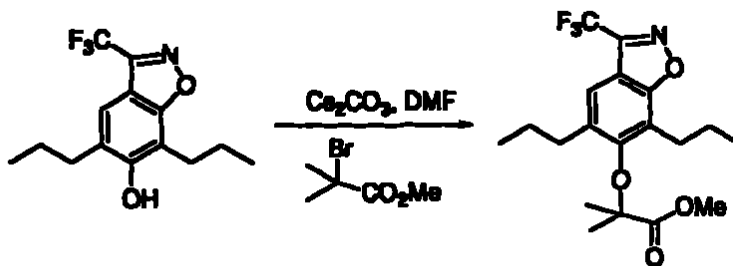


To a solution of Intermediate 2 (0.22 g, 0.89 mmol) and sulfuryl chloride (0.096 mL, 1.2 mmol) in CH_2Cl_2 (5 mL) was added Et_2O (0.5 mL). The reaction was stirred at room temperature overnight, partitioned between water and Et_2O . The organic layer was washed with saturated NaHCO_3 aqueous solution and brine, dried over MgSO_4 , filtered and concentrated in vacuo to give 7-chloro-6-hydroxy-5-propyl-3-trifluoromethyl-1,2-benzisoxazole. ^1H NMR (CDCl_3 , 400 MHz) δ 1.01 (t, 3H), 1.71 (m, 2H), 2.77 (t, 2H), 6.15 (s, 1H), 7.44 (s, 1H).

EXAMPLE 1

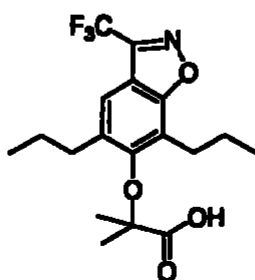


Preparation of methyl 2-(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy-2-methylpropanoate:

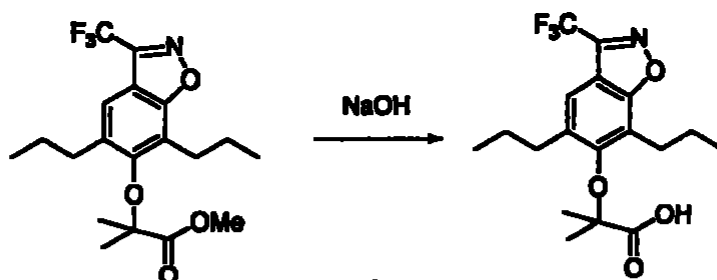


To a solution of starting phenol (20 g, 69.7 mmol) in DMF (200 mL) were added methyl α -bromoisobutyrate (126.7 g, 0.7 mol) and cesium carbonate (228g, 0.7 mol) and the mixture was stirred at 60 °C for seven days. Reaction was worked up by partitioning between ether and water. The aqueous phase was extracted with ether and the organic phase was washed with water, then brine, dried over Mg_2SO_4 , filtered, and evaporated in vacuo. Purification by chromatography gave the desired product. ^1H NMR ($CDCl_3$): δ 1.00 (m, 6H), 1.53 (s, 6H), 1.69 (m, 2H), 1.76 (m, 2H), 2.62 (t, 2H), 2.85 (m, 2H), 3.89 (s, 3H), 7.39 (s, 1H).

EXAMPLE 2

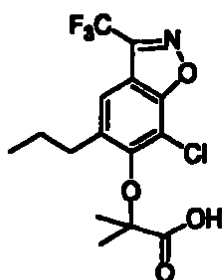


Preparation of 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid:

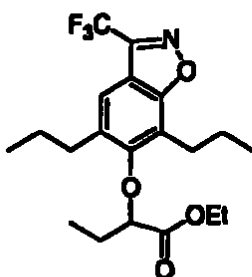


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To a solution of the starting methyl ester (8 g, 20.7 mmol) in methanol (50 mL) was added aqueous sodium hydroxide (1.0 N, 60 mL). Enough THF (100 mL) was added to bring the mixture back to a clear solution. The mixture was heated at 80 °C for 2 h. TLC showed that reaction was complete. The reaction was partitioned between 1N HCl and ether. The organic phase was washed with water and brine, dried over magnesium sulfate, filtered, and evaporated in vacuo. The solid residue was recrystallized from pentane to afford the desired product as colorless crystals. ^1H NMR ($CDCl_3$): δ 1.01 (m, 6H), 1.59 (s, 6H), 1.70 (m, 2H), 1.78 (m, 2H), 2.68 (t, 2H), 2.92 (m, 2H), 7.43 (s, 1H).

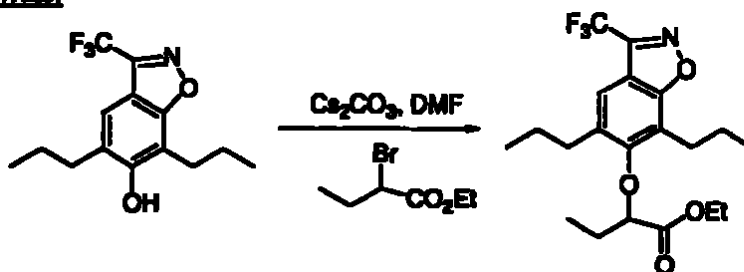
EXAMPLE 3

5 Similarly prepared as Example 2 using Intermediate 3. ¹H NMR (CDCl₃, 400 MHz) δ 1.03 (t, 3H), 1.68 (s, 6H), 1.72 (m, 2H), 2.75 (t, 2H), 7.52 (s, 1H).

EXAMPLE 4

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Preparation of ethyl 2-(5,7-dipropyl-3-(trifluoromethyl)-1,2-benzisoxazol-6-yl)oxybutyrate:

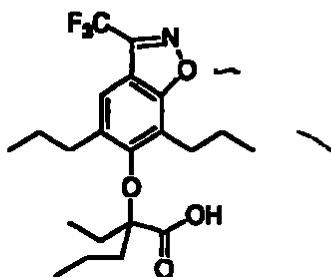


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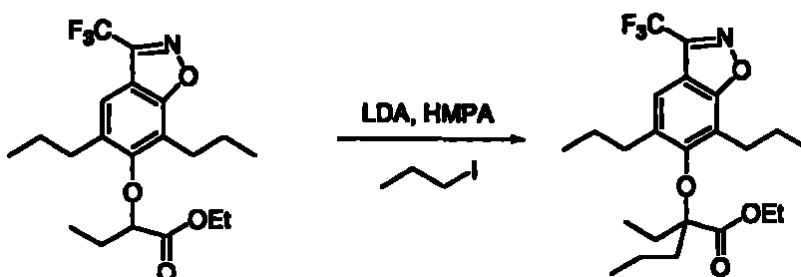
To a solution of Intermediate 1 (150 mg, 0.52 mmol) and ethyl 2-bromobutyrate (152 mg, 0.78 mmol) in DMF (5 mL) was added cesium carbonate (254 mg, 0.78 mmol). The mixture was stirred at room temperature for 6 h, then partitioned between ether and water. The organic phase was washed with water and

brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by flash chromatography gave the desired product. ^1H NMR(CDCl_3): δ 1.01 (m, 6H), 1.08 (t, 3H), 1.24 (t, 3H), 1.69 (m, 2H), 1.78 (m, 2H), 2.04 (m, 2H), 2.72 (m, 1H), 2.82 (m, 1H), 2.97 (m, 2H), 4.19 (m, 2H), 4.54 (m, 1H), 7.41 (s, 1H).

5

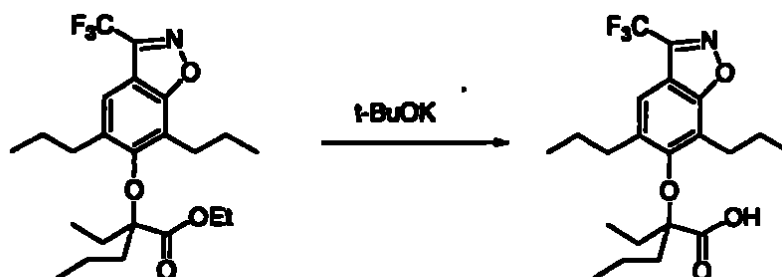
EXAMPLE 5

- 10 Step 1. Preparation of ethyl 2-((5,7-dipropyl-3-(trifluoromethyl)-1,2-benzisoxazol-6-yl)oxy)-2-ethylvalerate:



- 15 To a solution of the title compound of Example 5 (80 mg) in THF (5 mL) at -78°C was added LDA (1.5 M, 0.27 mL) followed by HMPA (0.069 mL). After 5 min at -78°C , iodopropane (98 μL) was introduced. The mixture was stirred at -78°C for 1 h, then allowed to slowly warm to room temperature over 2 h. Aqueous workup and purification by chromatography gave the desired product as a colorless oil. ^1H
- 20 NMR(CDCl_3): δ 0.87 (t, 3H), 0.95 (t, 3H), 1.01 (m, overlapping signals, 6H), 1.25 (m, 1), 1.50 - 1.80 (m, overlapping signals, 5H), 1.82 - 2.10 (m, overlapping signals, 4H), 2.68 (m, 2H), 2.91 (m, 2H), 4.18 (q, 2H), 7.38 (s, 1H).

Step 2. Preparation of 2-[5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl]oxy]-2-ethylvaleric acid:

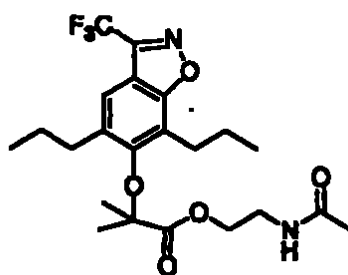


- 5

To a solution of the ethyl ester (30 mg) in DMSO (5 mL) at room temperature was added tBuOK (0.5 g). The reaction was stirred at room temperature overnight, partitioned between 1.0 N aqueous HCl and EtOAc. The organic phase was washed with water and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by preparative HPLC gave the desired product. ¹H NMR (CDCl₃) δ 0.87 (t, 3H), 0.95 (t, 3H), 1.01 (m, 6H), 1.25 (m, 1H), 1.56 - 1.77 (m, 5H), 1.82 - 2.10 (m, 4H), 2.69 (m, 2H), 2.91 (m, 2H), 7.42 (s, 1H).

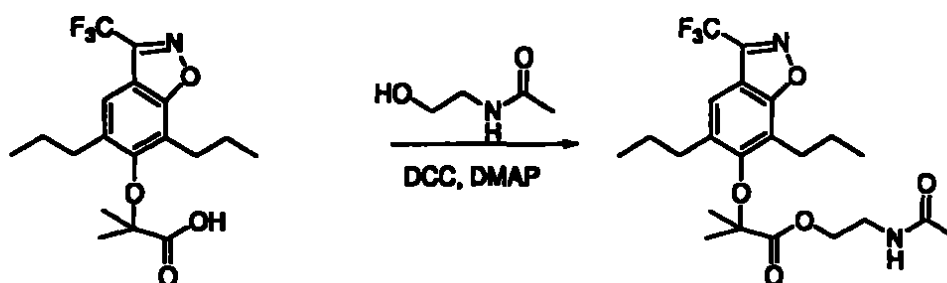
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EXAMPLE 6



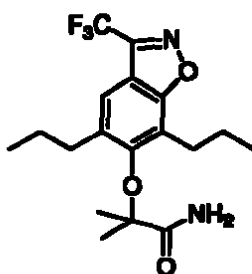
Preparation of 2-(acetamino)ethyl 2-[5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl]oxy]-2-methylpropanoate:

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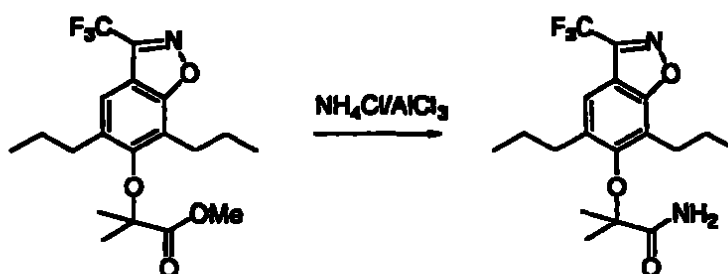


- To a solution of the title compound of Example 1 (500 mg, 1.34 mmol) in methylene chloride (10 mL) were added N-2-hydroxyethylacetamide (166 mg, 1.50 mmol), DCC (1.5 mL, 1N) and DMAP (16 mg, 0.13 mmol). The reaction was stirred at room temperature overnight. Precipitates were filtered off. Filtrate and washings were combined and evaporated in vacuo. Purification by flash chromatography gave the desired product. ¹H NMR (CDCl₃) δ 1.00 (m, 6H), 1.54 (s, 6H), 1.59 - 1.81 (m, 4H), 2.02 (s, 3H), 2.62 (t, 2H), 2.87 (m, 2H), 3.65 (m, 2H), 4.34 (t, 3H), 5.79 (s, broad, 1H), 7.40 (s, 1H).

EXAMPLE 7

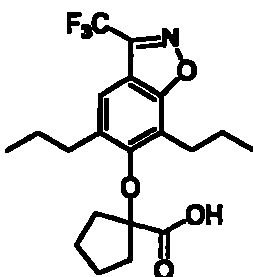


- Preparation of 2-((5,7-diisopropyl-3-(trifluoromethyl)-1,2-benzisoxazol-6-yl)oxy)-2-methylpropanamide:

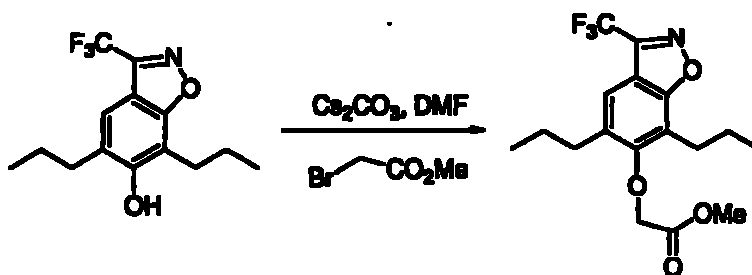


To a suspension of NH_4Cl (86 mg) in toluene (10 mL) at room temperature was added AlCl_3 (2.0 M, 0.8 mL) dropwise. The reaction was stirred for 3 h. The resultant clear solution was transferred to a solution of methyl 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionate (200 mg) in toluene (5 mL). The reaction was stirred at 80 °C overnight, cooled to room temperature, and then partitioned between EtOAc and 1.0 N aqueous HCl solution. The organic phase was washed with water and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by chromatography gave the desired product. ^1H NMR (CDCl_3) δ 1.00 (m, 6H), 1.51 (s, 6H), 1.65 (m, 2H), 1.75 (m, 2H), 2.70 (t, 2H), 2.94 (m, 2H), 5.72 (s, broad, 1H), 6.87 (s, broad, 1H), 7.43 (s, 1H).

EXAMPLE 8



Step 1. Preparation of methyl [(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]acetate:

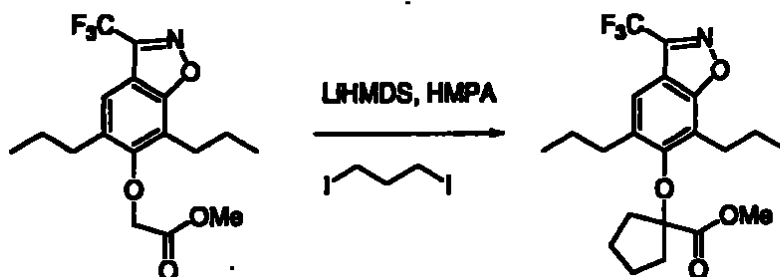


To a solution of starting phenol (0.5 g) in DMF (10 mL) were added methyl bromoacetate (0.4) and cesium carbonate (0.85) and the mixture was stirred at rt for 4 h. Reaction was worked up by partitioning between EtOAc and water. The organic

phase was washed with water, then brine, dried over Mg_2SO_4 , filtered, and evaporated in vacuo. Purification by chromatography gave the desired product. ^1H NMR (CDCl_3): δ 1.02 (m, 6H), 1.72 (m, 2H), 1.80 (m, 2H), 2.74 (t, 2H), 2.97 (m, 2H), 3.89 (s, 3H), 4.51 (s, 2H), 7.45 (s, 1H).

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Step 2. Preparation of methyl 1-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]cyclopentanecarboxylate:

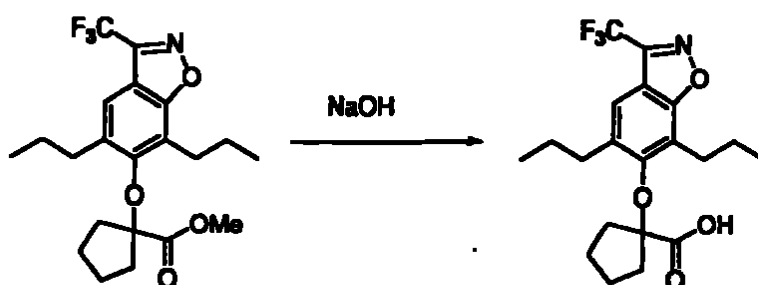


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To a solution of the starting ester (100 mg) in THF (4.0 mL) at -78°C were added LiHMDS (1.0 M, 0.31 mL) and HMPA (0.054 mL). After 15 min at -78°C , 1,4-diiodobutane (96 mg) was introduced. The reaction was allowed to warm to rt over 3 h, then cooled to -78°C before another 2.1 equiv of LiHMDS and HMPA were added. The reaction was allowed to slowly warm to rt and stirred overnight. The mixture was then partitioned between EtOAc and water. The organic phase was washed with water and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by chromatography gave the desired product. ^1H NMR (CDCl_3) δ 0.99 (m, 6H), 1.72 (m, 8H), 2.08 (m, 2H), 2.32 (m, 2H), 2.63 (t, 2H), 2.84 (t, 2H), 3.81 (s, 3H), 7.39 (s, 1H).

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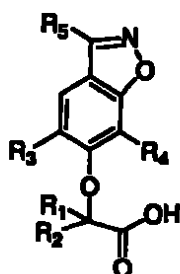
Step 3. Preparation of 1-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]cyclopentanecarboxylic acid:



To a solution of the starting methyl ester (30 mg) in methanol (2 mL) was added aqueous sodium hydroxide (1.0 N, 2 mL). Enough THF (6 mL) was added to bring the mixture back to a clear solution. The mixture was heated at 60 °C for 5 h, then partitioned between 1N HCl and ether. The organic phase was washed with water and brine, dried over magnesium sulfate, filtered, and evaporated in vacuo. Purification by chromatography gave the desired product. ¹H NMR (CDCl₃) δ 0.99 (m, 6H), 1.72 (m, 8H), 2.10 (m, 2H), 2.35 (m, 2H), 2.62 (t, 2H), 2.84 (t, 2H), 7.41 (s, 1H).

The examples listed in Table I below were prepared using the same or similar protocols as described for the examples (1 – 8) listed above.

TABLE I

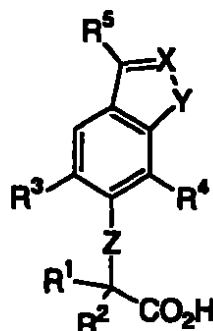


Example	R1	R2	R3	R4	R5	Partial ¹ H-Nmr Data (δ, ppm, CDCl ₃)
9	methyl	methyl	Cl	propyl	trifluoromethyl	1.67 (s, 6H), 7.70 (s, 1H)
10	ethyl	H	propyl	propyl	trifluoromethyl	4.60 (m, 1H), 7.44 (s, 1H)
11	ethyl	methyl	propyl	propyl	trifluoromethyl	1.15 (t, 3H), 1.28 (s, 3H), 7.43 (s, 1H)
12	propyl	methyl	propyl	propyl	trifluoromethyl	1.28 (s, 3H), 1.47 (m, 1H), 7.43 (s, 1H)
13	propyl	H	propyl	propyl	trifluoromethyl	4.64 (t, 1H), 7.43 (s, 1H)
14	propyl	propyl	propyl	propyl	trifluoromethyl	0.85 (t, 6H), 1.23 (m, 2H), 7.43 (s, 1H)
15	ethyl	ethyl	propyl	propyl	trifluoromethyl	1.96-1.86 (m, 4H), 7.41 (s, 1H)
16	methyl	H	Cl	propyl	ethyl	1.45 (t, 3H), 1.64 (d, 3H), 4.95 (q, 1H), 7.55 (s, 1H)
17	methyl	methyl	Cl	propyl	ethyl	1.45 (t, 3H), 2.97 (q, 3H), 7.53 (s, 1H)
18	methyl	H	Cl	propyl	trifluoromethyl	1.67 (d, 3H), 5.03 (q, 1H), 7.72 (s, 1H)
19	methyl	methyl	propyl	propyl	ethyl	1.45 (t, 3H), 3.00 (q, 2H), 7.29 (s, 1H)
20	methyl	methyl	propyl	propyl	methyl	2.57 (s, 3H), 7.27 (s, 1H)
21	methyl	methyl	propyl	propyl	methoxy	4.16 (s, 3H), 7.28 (s, 1H)
22	methyl	H	propyl	propyl	trifluoromethyl	1.61 (d, 3H), 4.71 (q, 1H), 7.46 (s, 1H)
23	methyl	H	propyl	propyl	phenyl	1.61 (d, 3H), 4.71 (q, 1H), 7.57 (s, 1H)
24	methyl	methyl	propyl	propyl	phenyl	7.54 (s, 1H), 7.58 (m, 3H), 7.96 (d, 2H)
25	methyl	ethyl	propyl	propyl	phenyl	1.16 (t, 3H), 1.30 (s, 3H), 7.54 (s, 1H)
26	H	H	propyl	propyl	trifluoromethyl	4.58 (s, 2H), 7.47 (s, 1H)
27	4-penten-1-yl	H	propyl	propyl	trifluoromethyl	4.62 (m, 1H), 5.03 (m, 2H), 5.80 (m, 1H), 7.43 (s, 1H)
28	cyclobutylidene		propyl	propyl	trifluoromethyl	2.37 (m, 2H), 2.58 (m, 2H), 7.50 (s, 1H)
29	cyclohexylidene		propyl	propyl	trifluoromethyl	1.20 (m, 1H), 2.30 (d, broad, 2H), 7.40 (s, 1H)

140

WHAT IS CLAIMED IS:

1. A compound having the formula I:



and pharmaceutically acceptable salts and prodrugs thereof, wherein

R^1 and R^2 are each independently selected from the group consisting of H, F, C₁₋₅ alkyl, C₂₋₅ alkenyl, and C₂₋₅ alkynyl, wherein said alkyl, alkenyl, and alkynyl may be linear or branched and are optionally substituted with 1-3 halogen atoms; or optionally R^1 and R^2 together form a C₃₋₆ cycloalkyl;

R^3 and R^4 are each independently selected from the group consisting of C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and chlorine, provided that R^3 and R^4 are not both chlorine, wherein said alkyl, alkenyl, and alkynyl groups may be linear or branched and are optionally substituted with 1-5 fluorine atoms;

X is N or CR;

Y is O, S, or NR;

Z is O or S;

Each R is independently selected from the group consisting of H, C₁₋₅ alkyl, C₂₋₅ alkenyl, and C₂₋₅ alkynyl, wherein said alkyl, alkenyl, and alkynyl may be linear or branched and are optionally substituted with 1-5 fluorine atoms and/or one -OC₁₋₃ alkyl, said -OC₁₋₃ alkyl being optionally substituted with 1-7 fluorine atoms;

5 and

R⁵ is selected from the group consisting of H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ Aryl, -OC₁₋₆ alkyl, -OC₂₋₆ alkenyl, -OC₂₋₆ alkynyl, -OC₆₋₁₀ Aryl, C₃₋₆ Cycloalkyl, 5-6-membered Heterocyclyl, 5-6-membered Heteroaryl, -OC₃₋₆ Cycloalkyl, -O 5-6-membered Heterocyclyl, -O 5-6 membered Heteroaryl, and a C₁₋₄ alkyl group which comprises at a position interrupting the chain or at the end of the chain a group selected from C₆₋₁₀ Aryl, C₃₋₆ Cycloalkyl, 5-6-membered Heterocyclyl, and 5-6-membered Heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, -Oalkyl, -Oalkenyl, and -Oalkynyl is optionally substituted with 1-5 fluorine atoms and/or one -OCH₃ or -OCF₃ group, and each of said Aryl, Cycloalkyl, Heteroaryl, Heterocyclyl, -OAryl, -OCycloalkyl, -OHeteroaryl, and -OHeterocyclyl groups is optionally substituted with 1-7 halogen atoms and/or one -OCH₃ or -OCF₃ group.

20 2. A compound having the formula I as recited in Claim 1, wherein X is N and Y is O.

3. A compound having the formula I as recited in Claim 1, wherein X is N and Y is S.

25 4. A compound having the formula I as recited in Claim 1, wherein X is N and Y is NR.

5. A compound having the formula I as recited in Claim 1, wherein X is CR and Y is O.

30 6. A compound having the formula I as recited in Claim 1, wherein X is CR and Y is S.

60183593-021800

142

7. A compound having the formula I as recited in Claim 1, wherein X is CR and Y is NR.

8. A compound having formula I as recited in any one of Claims 2 to 7, wherein

R⁵ is selected from the group consisting of H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, OC₁₋₅ alkyl, OC₂₋₅ alkenyl, OC₂₋₅ alkynyl, and phenoxy, wherein said alkyl, alkenyl, alkynyl, -Oalkyl, -Oalkenyl, and -Oalkynyl are optionally substituted with 1-5 fluorine atoms, and said phenoxy is optionally substituted with 1-5 halogens.

9. A compound as recited in Claim 8, wherein

R¹ and R² are each H or C₁₋₃ alkyl, where the number of carbon atoms in R¹ and R² together is 0-5;

R³ and R⁴ are each independently C₁₋₅ alkyl;

R⁵ is selected from the group consisting of C₁₋₅ alkyl and -OC₁₋₅ alkyl, wherein said alkyl and -Oalkyl are optionally substituted with 1-5 fluorine atoms, and

Z is O.

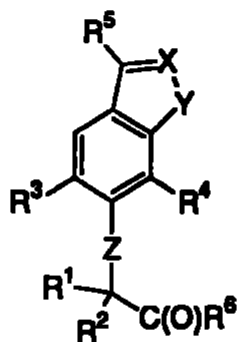
10. A compound as recited in Claim 9, wherein R⁵ is C₁₋₃ alkyl, -OC₁₋₃ alkyl, CP₃, C₂F₅, -OCF₃ or -OC₂F₅; and

R³ and R⁴ are each n-propyl.

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143

11. A compound having Formula Ia,



Ia

wherein R⁶ is a group that is easily removed under physiological conditions during or after administration to a mammalian patient to yield a compound having Formula I, or the carboxylate anion thereof, or a pharmaceutically acceptable salt thereof, as recited in Claim 1; and

wherein R¹, R², R³, R⁴, R⁵, X, Y, Z, and R are as defined in Claim 1.

12. A compound as recited in Claim 11, wherein R⁶ is selected from the group consisting of -OR⁷, -OCH₂OR⁷, -OCH(CH₃)OR⁷, -OCH₂OC(O)R⁷, -OCH(CH₃)OC(O)R⁷, -OCH₂OC(O)OR⁷, -OCH(CH₃)OC(O)OR⁷, -NR⁸R⁸, and -ONR⁸R⁸,

wherein each R⁷ is independently selected from C₁₋₆ alkyl optionally substituted with one or two groups selected from -CO₂H, -CONH₂, -NH₂, -OH, -OAc, NHAc, and phenyl; and

wherein each R⁸ is independently selected from H and R⁷.

13. A compound represented by any of the structures of Examples 1-29.

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144

14. A pharmaceutical composition comprising a compound of any one of Claims 1-13 and a pharmaceutically acceptable carrier.

5 15. A method for treating, controlling, or preventing non-insulin dependent (Type 2) diabetes mellitus in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

10 16. A method for treating, controlling or preventing hyperglycemia in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

15 17. A method for treating, controlling or preventing lipid disorders, hyperlipidemia, or low HDL in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

20 18. A method for treating, controlling or preventing obesity in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

25 19. A method for treating, controlling or preventing hypercholesterolemia in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

30 20. A method for treating, controlling or preventing hypertriglyceridemia in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

35 21. A method for treating, controlling or preventing dyslipidemia and/or low HDL cholesterol in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

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145-~~145~~

22. A method for treating, controlling or preventing atherosclerosis in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

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23. A method of treating, controlling or preventing one or more diseases, disorders, or conditions selected from the group consisting of (1) non-insulin dependent diabetes mellitus (NIDDM), (2) hyperglycemia, (3) low glucose tolerance, (4) insulin resistance, (5) obesity, (6) lipid disorders, (7) dyslipidemia, (8) hyperlipidemia, (9) hypertriglyceridemia, (10) hypercholesterolemia, (11) low HDL levels, (12) high LDL levels, (13) atherosclerosis and its sequelae, (14) vascular restenosis, (15) irritable bowel syndrome, (16) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (17) other inflammatory conditions, (18) pancreatitis, (19) abdominal obesity, (20) neurodegenerative disease, (21) retinopathy, (22) neoplastic conditions, (23) adipose cell tumors, (24) adipose cell carcinomas, such as liposarcoma, (25) prostate cancer and other cancers, including gastric, breast, bladder and colon cancers, (26) angiogenesis, (27) Alzheimer's disease, (28) psoriasis, (29) high blood pressure, (30) Syndrome X, (31) ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component, said method comprising the administration of an effective amount of a compound of Claim 1.

24. A method of treating, controlling or preventing one or more diseases, disorders, or conditions selected from the group consisting of (1) diabetes mellitus, and especially non-insulin dependent diabetes mellitus (NIDDM), (2) hyperglycemia, (3) low glucose tolerance, (4) insulin resistance, (5) obesity, (6) lipid disorders, (7) dyslipidemia, (8) hyperlipidemia, (9) hypertriglyceridemia, (10) hypercholesterolemia, (11) low HDL levels, (12) high LDL levels, (13) atherosclerosis and its sequelae, (14) vascular restenosis, (15) irritable bowel syndrome, (16) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (17) other inflammatory conditions, (18) pancreatitis, (19) abdominal obesity, (20) neurodegenerative disease, (21) retinopathy, (22) neoplastic conditions, (23) adipose cell tumors, (24) adipose cell carcinomas, such as liposarcoma, (25)

60183593-021800

750
146

501835 3-021800

- prostate cancer and other cancers, including gastric, breast, bladder and colon cancers, (26) angiogenesis, (27) Alzheimer's disease, (28) psoriasis, (29) high blood pressure, (30) Syndrome X, (31) ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component, said method
- 5 comprising the administration of an effective amount of a compound of Claim 1, and an effective amount of one or more other compounds selected from the group consisting of:
- (a) insulin sensitizers including (i) PPAR γ agonists such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone, and
- 10 the like), and compounds disclosed in WO97/27857, 97/28115, 97/28137 and 97/27847; (ii) biguanides such as metformin and phenformin; (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors, and (iv) dipeptidyl peptidase IV (DP-IV) inhibitors;
- (b) insulin or insulin mimetics;
- 15 (c) sulfonylureas such as tolbutamide and glipizide, or related materials;
- (d) α -glucosidase inhibitors (such as acarbose);
- (e) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin,
- 20 itavastatin, ZD-4522 and other statins), (ii) sequestrants (cholestyramine, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) nicotinic alcohol, nicotinic acid or a salt thereof, (iv) PPAR α agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and benzaifibrate), (v) PPAR α/γ dual agonists, such as KRP-297, (vi) inhibitors of cholesterol absorption,
- 25 such as for example beta-sitosterol, (vii) acyl CoA:cholesterol acyltransferase inhibitors, such as for example avasimibe, and (viii) anti-oxidants, such as probucol;
- (f) PPAR δ agonists such as those disclosed in WO97/28149;
- (g) antiobesity compounds such as fenfluramine, dexfenfluramine, phentramine, sulbitramine, orlistat, neuropeptide Y5 inhibitors, and β_3 adrenergic
- 30 receptor agonists;
- (h) an ileal bile acid transporter inhibitor; and
- (i) agents intended for use in inflammatory conditions such as aspirin, non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, and cyclo-oxygenase 2 selective inhibitors.
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147

25. A method for the treatment, control, or prevention of one or more conditions selected from hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia, and dyslipidemia, which method comprises administering to a mammalian patient in need of such treatment a therapeutically effective amount of a dual PPAR α / γ agonist.

26. The method as recited in Claim 25, wherein the dual PPAR α / γ agonist is administered with an HMG-CoA reductase inhibitor.

27. The method as recited in Claim 26, wherein the HMG-CoA reductase inhibitor is a statin.

28. The method as recited in Claim 27, wherein the statin is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, itavastatin, ZD-4522 and rivastatin.

29. A method for the treatment, control, or prevention of one or more conditions selected from inflammatory conditions, inflammatory bowel disease, Crohn's disease, and ulcerative colitis, which method comprises administering to a mammalian patient in need of such treatment a therapeutically effective amount of a PPAR agonist.

30. The method as recited in Claim 29, wherein said PPAR agonist is a dual PPAR α / γ agonist.

31. The method as recited in Claim 30, wherein the dual PPAR α / γ agonist is administered with an HMG-CoA reductase inhibitor.

32. The method as recited in Claim 31, wherein the dual PPAR α / γ agonist is a compound according to Claim 1 and the HMG-CoA reductase inhibitor is a statin selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, itavastatin, ZD-4522 and rivastatin.

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148

33. A method for treating, preventing or controlling atherosclerosis in a mammalian patient in need of such treatment comprising the administration to said patient of an effective amount of a compound of Claim 1 and an effective amount of an HMG-CoA reductase inhibitor.

34. A pharmaceutical composition for the treatment, prevention or control of atherosclerosis, comprising: (1) a compound according to Claim 1, (2) an HMG-CoA reductase inhibitor, and (3) a pharmaceutically acceptable carrier.

35. A pharmaceutical composition comprising (1) a compound according to Claim 1, (2) one or more compounds selected from the group consisting of:

(a) insulin sensitizers including (i) PPAR γ agonists such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone, and the like), and compounds disclosed in WO97/27857, 97/28115, 97/28137 and 97/27847; (ii) biguanides such as metformin and phenformin; (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors, and (iv) dipeptidyl peptidase IV (DP-IV) inhibitors;

(b) insulin or insulin mimetics;

(c) sulfonylureas such as tolbutamide and glipizide, or related materials;

(d) α -glucosidase inhibitors (such as acarbose);

(e) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, ZD-4522 and other statins), (ii) sequestrants (cholestyramine, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) nicotinic alcohol, nicotinic acid or a salt thereof, (iv) PPAR α agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and benzafibrate), (v) PPAR α/γ dual agonists, such as KRP-297, (vi) inhibitors of cholesterol absorption, such as for example beta-sitosterol, (vii) acyl CoA:cholesterol acyltransferase inhibitors, such as for example avasimibe, and (viii) anti-oxidants, such as probucol;

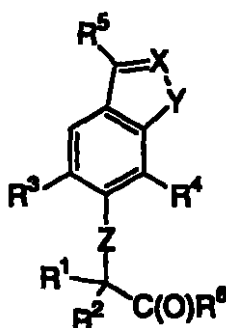
(f) PPAR δ agonists such as those disclosed in WO97/28149;

(g) antiobesity compounds such as fenfluramine, dexfenfluramine, phentermine, sulbitramine, orlistat, neuropeptide Y5 inhibitors, and β_3 adrenergic receptor agonists;

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- (h) an ileal bile acid transporter inhibitor; and
 (i) agents intended for use in inflammatory conditions such as aspirin,
 non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, and cyclo-
 oxygenase 2 selective inhibitors; and
 5 (3) a pharmaceutically acceptable carrier.

36. A compound having Formula Ia,



Ia

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and pharmaceutically acceptable salts thereof, wherein

- R¹ and R² are each independently selected from the group consisting
 of H, F, C₁₋₅ alkyl, C₂₋₅ alkenyl, and C₂₋₅ alkynyl, wherein said alkyl, alkenyl, and
 15 alkynyl may be linear or branched and are optionally substituted with 1-3 halogen
 atoms; or optionally R¹ and R² together form a C₃₋₆ cycloalkyl;

- R³ and R⁴ are each independently selected from the group consisting
 of C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, and chlorine, provided that R³ and R⁴ are
 20 not both chlorine, wherein said alkyl, alkenyl, and alkynyl groups may be linear or
 branched and are optionally substituted with 1-5 fluorine atoms;

X is N or CR;

25

Y is O, S, or NR;

150

Z is O or S;

Each R is independently selected from the group consisting of H, C₁₋₅ alkyl, C₂₋₅ alkenyl, and C₂₋₅ alkynyl, wherein said alkyl, alkenyl, and alkynyl may be linear or branched and are optionally substituted with 1-5 fluorine atoms and/or one -OC₁₋₃ alkyl, said -OC₁₋₃ alkyl being optionally substituted with 1-7 fluorine atoms;

R⁵ is selected from the group consisting of H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ Aryl, -OC₁₋₆ alkyl, -OC₂₋₆ alkenyl, -OC₂₋₆ alkynyl, -OC₆₋₁₀ Aryl, C₃₋₆ Cycloalkyl, 5-6-membered Heterocyclyl, 5-6-membered Heteroaryl, -OC₃₋₆ Cycloalkyl, -O 5-6-membered Heterocyclyl, -O 5-6 membered Heteroaryl, and a C₁₋₄ alkyl group which comprises at a position interrupting the chain or at the end of the chain a group selected from C₆₋₁₀ Aryl, C₃₋₆ Cycloalkyl, 5-6-membered Heterocyclyl, and 5-6-membered Heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, -Oalkyl, -Oalkenyl, and -Oalkynyl is optionally substituted with 1-5 fluorine atoms and/or one -OCH₃ or -OCF₃ group, and each of said Aryl, Cycloalkyl, Heteroaryl, Heterocyclyl, -OAryl, -OCycloalkyl, -OHeteroaryl, and -OHeterocyclyl groups is optionally substituted with 1-7 halogen atoms and/or one -OCH₃ or -OCF₃ group;

R⁶ is selected from the group consisting of -OR⁷, -OCH₂OR⁷, -OCH(CH₃)OR⁷, -OCH₂OC(O)R⁷, -OCH(CH₃)OC(O)R⁷, -OCH₂OC(O)OR⁷, -OCH(CH₃)OC(O)OR⁷, -NR⁸R⁸, and -ONR⁸R⁸;

Each R⁷ is independently selected from C₁₋₆ alkyl optionally substituted with one or two groups selected from -CO₂H, -CONH₂, -NH₂, -OH, -OAc, NHAc, and phenyl; and

Each R⁸ is independently selected from H and R⁷.

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TITLE OF THE INVENTION

ARYLOXYACETIC ACIDS FOR DIABETES AND LIPID DISORDERS

ABSTRACT OF THE DISCLOSURE

- 5 A class of aryloxyacetic acids comprises compounds that are potent agonists of PPAR alpha and/or gamma, and are therefore useful in the treatment, control or prevention of non-insulin dependent diabetes mellitus (NIDDM), hyperglycemia, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, obesity, vascular restenosis, inflammation, and
- 10 other PPAR alpha and/or gamma mediated diseases, disorders and conditions.

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DE UN DOCUMENTO ESCRITO EN INGLES

PATENTE

Caso Merck Conjunto 20630Y

No. de Serie EU

Fecha de Presentación

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Por el valor recibido por el presente, nosotros, KUN LIU, LIBO XU Y A. BRIAN JONES, domiciliados en 39 WINDING BROOK WAY, EDISON, NUEVA JERSEY 08820, 2106 DAHLIA CIRCLE, DAYTON, NUEVA JERSEY 08810; Y ROSSIE, MIDDLE STREET, CLAVERING, ESSEX, GB,

vendemos, cedemos y traspasamos a MERCK & CO., Inc., una sociedad del Estado de Nueva Jersey, con oficinas en Lincoln Avenue, Ciudad de Rahway, Estado de Nueva Jersey, a sus sucesores, cesionarios y representantes legales, el pleno derecho, título e interés, en todos los países en y sobre ciertas invenciones relacionadas con

ACIDOS ARILOXIACETICOS PARA DIABETES Y DESORDENES LÍPIDOS

según se describe en la solicitud para Carta de Patente de los Estados Unidos, firmada por nosotros en la misma fecha del presente, y en la(s) solicitud(es) provisional(es)

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Resol. No. 0177 del 97 MinJusticia

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153

hayan sido otorgadas, y bajo cualquiera y todas las extensiones, divisionales, reexpediciones y continuaciones de dichas Cartas de Patentes.

Solicitamos que cualquiera y todas las Patentes para dichas invenciones sean expedidas a nombre de dicho cesionario, sus sucesores, cesionarios y representantes legales. o a quienes pueda designar.

Aceptamos que, cuando sea solicitado, nosotros, sin cargo para dicho cesionario pero con los costos a su cargo, firmaremos todos los documentos, tomaremos todos los juramentos de ley, y realizaremos todos los actos que sean necesarios, requeridos o convenientes para asegurar y mantener las Patentes para dichas invenciones en cualquiera y todos los países y para transferir el título de propiedad de éstas en dicho cesionario, sus sucesores, cesionarios y representantes legales o designados.

Nosotros aceptamos con dicho cesionario, sus sucesores, cesionarios y representantes legales, que los derechos y la propiedad aquí convenidos se encuentran libres de cualquier gravamen y que tenemos el pleno derecho para convenir lo aquí expresado.

Por el presente autorizamos a nuestro abogado, James L. McGinnis o al abogado con poder en esta solicitud de la mencionada MERCK & CO., Inc., para insertar el No. de Serie y la Fecha de Presentación de dicha(s) solicitud(es) cuando sean conocidas.

Firmado en Rahway, Nueva Jersey 07065 este 2 de Febrero de 2001.

(Firma) _____
KUN LIU

(Firma) _____
LIBO XU

Angela A. Pulecio
ANGELA A. PULECIO MAYORCA
Traductor e Int. :: Oficial
Resol. No. 0177 de 1997 Min. Justicia

154

Caso Merck Conjunto 20630Y

No. de Serie EU

Fecha de Presentación

CESION Y ACUERDO

Firmado en _____ este _____ de _____.

(Firma) _____

A. BRIAN JONES

ESTADO DE NUEVA JERSEY }

SS.

Condado de Union }

Personalmente se presentó ante mí KUN LIU LIBO XU

conocido por mí y por mí conocido como la(s) persona(s) que firmó(arón) el instrumento anterior y reconoció dicho instrumento como un acto libre y voluntario este 2 de Febrero de 2001.

(Firma) _____

Notario Público

Sello: DIANE S. WALSH

NOTARIO PUBLICO DE NUEVA JERSEY

Mi Comisión expira 5/7/2003

Angela D. Pulido
ANGELA D. PULIDO
Traductor Público Oficial
Resol. No. 617 del/97 MinJusticia

REINO UNIDO }

SS.

Condado de _____ }

Personalmente se presentó ante mí el nombrado A. BRIAN JONES

conocido por mí y por mí conocido como la(s) persona(s) que firmó(aron) el instrumento anterior y reconoció dicho instrumento como un acto libre y voluntario este 13 de Febrero de 2001.

(Firma) _____

Notario Público

Mi comisión expira a la muerte

Sello: STEPHEN B. THIRSK

NOTARIO PUBLICO

GATE HOUSE THE HIGH

HARLOW, ESSEX CM20 1LW

INGLATERRA

SELLO (ilegible)

ESTADO DE NUEVA JERSEY)

) SS.

Condado de Union)

Angela Filice
ANGELA FILICE
Traductora Oficial
Resol. No. 0117 del 1991

Yo, BARBARA ANN COZZI, un NOTARIO PUBLICO del ESTADO DE
NUEVA JERSEY, CERTIFICO que he examinado la Cesión y Acuerdo original, Caso

20630Y, titulado "ACIDOS ARILOXIACETICOS PARA DIABETES Y DESORDENES LÍPIDOS", y que adjunto se encuentra una copia verdadera de ello.

(Firma) _____

NOTARIO PUBLICO

Sello: BARBARA ANN COZZI

Notario Público de Nueva Jersey

Mi comisión expira el 30 de Noviembre de 2003

Fecha: 26 de Febrero de 2001

Caso No. 20603Y

Sello en Relieve: BARBARA ANN COZZI , NOTARIO PÚBLICO, NUEVA JERSEY

APOSTILLA

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

1. **PAÍS: ESTADOS UNIDOS DE AMÉRICA**
2. **ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:**
BARBARA ANN COZZI
3. **ACTUANDO EN SU CAPACIDAD DE:**
NOTARIO PÚBLICO DE NUEVA JERSEY
4. **POSEE EL SELLO/ESTAMPILLA DE:**
BARBARA ANN COZZI, NOTARIO

Angela A. Puleo
ANGELA A. PULEO MAYORGA
Traductor C. I. Oficial
Resol. No. 0-17 de la Justicia

CERTIFICADO

162
157

5. En TRENTON, NUEVA JERSEY
 6. El 15 DE MARZO DE 2001
 7. Por Peter R. Lawrance, TESORERO DE NUEVA JERSEY
 8. No. A129102
 9. SELLO/ESTAMPILLA
- (Sello Dorado): SELLO DEL ESTADO DE NUEVA JERSEY

10. FIRMA
(Firma)

=====

Es traducción fiel y completa, de la cual queda copia en el archivo del Traductor para su confrontación, a la cual me remito.

Bogotá, D.C., 26 de Marzo de 2001

=====

Angela A. Pulecio Mayorga
ANGELA A. PULECIO MAYORGA
Traductor é l. oficial
Resol. No. 0177 del 2001 Indjusticia

84

Cuevas
MINISTERIO DE RELACIONES
EXTERIORES
Pistean
421018

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPLEA
LAS FUENTES

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2001 MAR 27 10:54

Jefe de Legalizaciones
SANTAFE DE BOGOTA D.C.

APOSTILLE

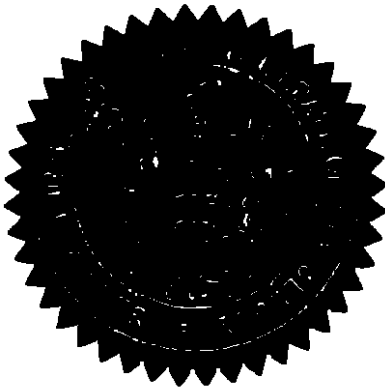
158

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

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

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 15TH DAY OF MARCH 2001
7. BY: Peter R Lawrance, NEW JERSEY TREASURER
8. NO. A129102
9. SEAL/STAMP:
10. SIGNATURE



Peter R Lawrance

ASSIGNMENT AND AGREEMENT

U.S. Serial No. _____

Filing Date _____

For value received, we, KUN LIU, LIBO XU AND A. BRIAN JONES

160

of 39 WINDING BROOK WAY, EDISON, NEW JERSEY 08820, 2106 DAHLIA CIRCLE, DAYTON, NEW JERSEY 08810;
AND ROSSIE, MIDDLE STREET, CLAVERING, ESSEX, GB

hereby sell, assign and transfer to MERCK & CO., Inc., a corporation of the State of New Jersey, having an office at Lincoln Avenue,
City of Rahway, State of New Jersey, and its successors, assigns and legal representatives, the entire right, title and interest, for all
countries, in and to certain inventions relating to

ARYLOXYACETIC ACIDS FOR DIABETES AND LIPID DISORDERS

described in an application for Letters Patent of the United States, executed by us on even date herewith, and in provisional application(s)

Serial No. 60/183,593 filed on 02/18/2000 ; Serial No. _____ filed on _____ ; Serial No. _____ filed on _____

(if applicable), and all the rights and privileges, including any and all benefits under the International Convention for the Protection of
Industrial Property under any and all Letters Patents which may be granted therefor, and under any and all extensions, divisionals,
reissues and continuations of said Letters Patents.

We request that any and all Patents for said inventions be issued to said assignee, its successor, assigns and legal
representatives, or to such nominees as it may designate.

We agree that, when requested, we will, without charge to said assignee but at its expense, sign all papers, take all rightful
oaths, and do all acts which may be necessary, desirable or convenient for securing and maintaining Patents for said inventions in any
and all countries and for vesting title thereto in said assignee, its successors, assigns and legal representatives or nominees.

We covenant with said assignee, its successors, assigns and legal representatives, that the rights and property herein conveyed
are free and clear of any encumbrance, and that we have full right to convey the same as herein expressed.

We hereby authorize our attorney, James L. McGinnis or an attorney with Power of Attorney in this application,

to insert Serial No., and Filing Date of said application(s) when known.

Signed at Rahway, New Jersey 07065 this 2nd day of February, 2001.

Kun Liu
KUN LIU

Libo Xu
LIBO XU

ASSIGNMENT AND AGREEMENT

Signed at _____ this _____ day of _____

A. BRIAN JONES

STATE OF NEW JERSEY

County of UNION

SS.

Personally appeared before me the above-named KUN LIU LIBO XU

to me known and known to me to be the person(s) who executed the foregoing instrument and acknowledged said instrument to be their free act and deed this 2nd day of February, 2001.

Diane S. Walsh

Notary Public

Un. Kingdom

County of Essex

SS.

DIANE S. WALSH
NOTARY PUBLIC OF NEW JERSEY
Commission Expires 5/7/2003

Personally appeared before me the above-named A. BRIAN JONES

to me known and known to me to be the person(s) who executed the foregoing instrument and acknowledged said instrument to be their free act and deed this 13th day of February, 2001.STEPHEN B. THIRSK
NOTARY PUBLICGATE HOUSE THE HIGH
HARLOW, ESSEX CM20 1LW
ENGLAND

S.B. Thirsk

Notary Public

My commission expires
on death



2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 167

Radicación no 01-11989

Concepto Técnico no 1797

Clasificación Internacional de Patentes: A 61 K 31/423// C07D263/54

Practicado el examen de acuerdo a lo establecido en el Art. 38 de la Decisión 486 se determinó que esta solicitud de Patente de Invención:

- SI ☒ NO ☐ Contiene un resumen de la invención (Art.26-e).
- SI ☒ NO ☐ Contiene el título o nombre de la invención (Art.27-d).
- SI ☒ NO ☐ Contiene la descripción de la invención (Art.26-b).
- SI ☒ NO ☐ NO ES APLICABLE ☐ Contiene los dibujos necesarios para comprender la invención (Art.26-d)
- SI ☒ NO ☐ Contiene una o más reivindicaciones. (Art.26-c).
- SI ☐ NO ☐ NO ES APLICABLE ☒ Han sido desarrollados los productos y/o procedimientos a partir de recursos genéticos o de sus productos derivados de los que cualquiera de los Países Miembros es país de origen. (Art. 26- h).
- SI ☐ NO ☐ NO ES APLICABLE ☒ Los productos y/o procedimientos han sido obtenidos o desarrollados a partir de los conocimientos tradicionales de las comunidades indígenas, afroamericanas, o locales de los países miembros, de acuerdo a lo establecido en la Decisión 381 y sus modificaciones y reglamentaciones vigentes.(Art.26-f).
- SI ☐ NO ☒ La invención se refiere a un producto relativo a un material biológico. (Art.26-J).
- SI ☒ NO ☐ La prioridad coincide con la materia reivindicada.
- SI ☒ NO ☐ **CUMPLE LOS REQUISITOS TÉCNICOS**

OBSERVACIONES Y OTROS: SI ☐ NO ☒ ver hoja(s) anexa(s)

EXAMINADOR TÉCNICO
202049

Bogotá D. C., 11 de Diciembre de 2002

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 394 12 21-2-3-4
Fax: 281 31 25 e-mail: info@sic.gov.co
Santa Fe de Bogotá D.C. - Colombia



Folio: 188

2020
Bogotá DC

Doctor
JOSE ANTONIO LLOREDA
Apoderado

REFERENCIA:	Radicación No.	01-11989
	Trámite	002
	Evento	001
	Actuación	416
	Oficio No.	2315
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la misma Decisión.

Cúmplase
Dado en Bogotá DC, a los 28 D.C. 2022


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

526

202049

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 28 e-mail: info@dic.gov.co
Santa Fe de Bogotá D.C. - Colombia

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 01-11989

**EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION
FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 526, DE
FECHA 31 DE MARZO DE 2003, EL TERMINO HABIL SEÑALADO POR LA LEY
EXPIRA EL 01 DE JULIO DE 2003.**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI

NO **X**

Bogotá D.C., Octubre 08 de 2003

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

165

RADICACIÓN: 1-11989

EDICTO No. 17459

LA SECRETARÍA GENERAL AD-HOC HACE SABER:

Que esta Superintendencia profirió Resolución No. 28798 de 22-OCT-2003. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

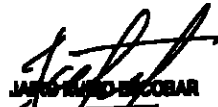
ARTICULO PRIMERO: Declarar abandonada la solicitud de privilegio de patente de invención contenida en el expediente de la referencia.

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor José Antonio Lloreda, o a quien haga sus veces, quien actúa como apoderado de Merch & Co., Inc., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a las 22 OCT 2003

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIRO RUEDA ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc 08-NOV-2003  Esta edicto se desfija hoy 20-NOV-2003 a las cinco (5:00 p.m.) 
Secretaría General Ad-Hoc
EDICTO No. 17459