

87
85.

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINDUSTRIA Y COMERCIO

Radicacion : 00065017 00000001

Folios: 135

Fecha (MM): 2000-10-27 16:15:01

Tramite : 002 PATENTES 3 1 REGISTRO/ 329 COMPLETEN

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Re: P1.-ABBOTT LABORATORIES.-Solicitud de Patente de Invención para "ANTAGONISTAS DE LOS RECEPTORES DE L S GLUCOCORTICOIDES PARA EL TRATAMIENTO DE LA DIABETES".-Clase A.61.-Expediente número 00-065.017.-

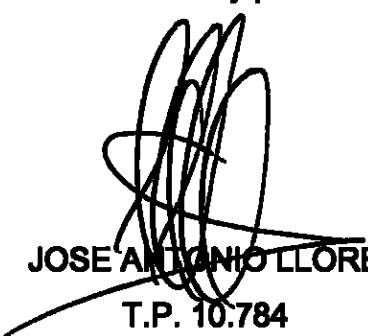
1. Me refiero a mi solicitud de patente arriba nombrada de fecha 30 de Agosto de 2000.

2. Anexos me permito presentar a usted:

- (1) Copia autentica de la primera solicitud de patente presentadas para el invento arriba nombrado respecto de la cual reclamo prioridad, a saber la solicitud estadinense número 09/388.251 de 1 de Septiembre de 1999, junto con su traducción oficial No. LLC-075-2000, correspondiente a las legalizaciones y reivindicaciones de dicho documento;
- (2) Copias debidamente autenticadas 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 la solicitud estadinense número 09/388.251, respecto de la cual se reivindica prioridad en el presente caso;
- (3) Documento que acredita el traspaso que los autores del invento de la referencia hacen a favor de mi representado, de sus derechos sobre el mismo, debidamente legalizado hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 447123 de 4 de Octubre de 2000; y
- (4) Traducción Oficial No. 0302, debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 547023 de 10 de Octubre de 2000, correspondiente a dicho documento de traspaso.

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

Señor Superintendente,



JOSE ANTONIO LLOREDA

T.P. 10.784

Código 231

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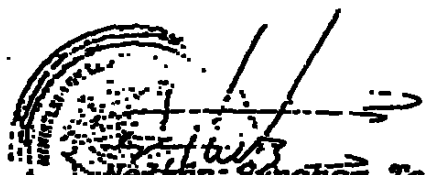
EL SUSCRITO JEFE DEL AREA DE
LEGALIZACIONES DE MINISTERIO DE
RELACIONES EXTERIORES

HACE CONSTAR

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

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

Dada en Santafé de Bogotá, D.C., a los diez y nueve días
(19) del mes de diciembre de 1994.


Nelson Sánchez Torres
Jefe Área de Legalizaciones

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFÉ DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA CONCEDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFÉ DE BOGOTÁ, 02 JUL 1998
PABLO MENDEZ SARAJAS
NOTARIO

NSI/gcm.

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFÉ DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA CONCEDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFÉ DE BOGOTÁ, 01 JUL 1998
PABLO MENDEZ SARAJAS
NOTARIO

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFÉ DE BOGOTÁ
HAGO CONSTAR
QUE LA FOTOCOPIA CONCEDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFÉ DE BOGOTÁ, 01 JUL 1998
JUAN MANUEL POTERO MEDINA
NOTARIO



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 INGLÉS-ESPAÑOL, ESPAÑOL-INGLÉS a GABRIEL RUEDA CHADD, identificado con la cédula de ciudadanía No. 17.124.145 expedida en Bogotá. Que dicha resolución se encuentra vigente en la fecha.

A solicitud del interesado, en Santafé de Bogotá D.C., a los 17 días del mes de noviembre de 1994.

JORGE LOIS SARDAGAL SARDAGAL

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA
101 SET 2000
PAOLO MENDEZ BARRAJAS

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA
17 AGO 1998

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA
23 NOV 1998

SECRETARIO
GENERAL
JUAN MANUEL BOTOLINO MEDINA
NO. 2210
COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA
06 ENE 1999
JUAN MANUEL BOTOLINO MEDINA
NOTARIO

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA
13 SET 1998
PAOLO MENDEZ BARRAJAS

LR/mmc

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TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL DE SANTAFE DE BOGOTA
SECRETARIA GENERAL

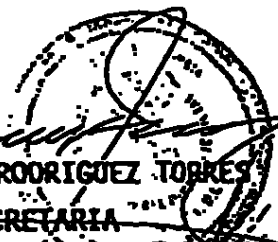
LA SUSCRITA SECRETARIA DEL H. TRIBUNAL SUPERIOR DEL DISTRITO JUDICIAL
DE SANTAFE DE BOGOTA,

CERTIFICA:

Que el Acuerdo No. 183 de diciembre 3 de 1982 emanado de esta Corporación, por medio del cual dió posesión al señor GABRIEL RUEDA CHADAYAN identificado con Cédula de Ciudadanía número 17.124.145 de Bogotá como TRADUCTOR E INTERPRETE OFICIAL de los idiomas INGLES-ESPAÑOL-ESPAÑOL-INGLES, en virtud de la Resolución No. 5996, se sigue vigente.

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


MARIA INES RODRIGUEZ TORRES
SECRETARIA



COMO NOTARIO SEXTO ENCARGADO
DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 12 SET 1998
PABLO MENDEZ BARAJAS

CTM./

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 01 SET 1998
PABLO MENDEZ BARAJAS

AGO. 1998

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 01 JUL 1998
JUAN MANUEL BOTERO MEDINA
NOTARIO

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA CONCORDA CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 23 NOV 1998
JUAN MANUEL BOTERO MEDINA
NOTARIO

REF: LLC-075-2000. 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

Agosto 21 del 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: 09/388.251

Fecha de presentación: Septiembre 01, 1999

Por autorización del

COMISIONADO DE MARCAS REGISTRADAS Y PATENTES

W. MONTGOMERY

Funcionario Encargado de Certificaciones (Hay firma y sello)

2591

Oficina de Marcas y Patentes:
DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

TRANSMISION UTILITARIA DE LA SOLICITUD DE PATENTE

(Solamente para nuevas solicitudes no provisionales según lo dispone la Sección 37 C.F.R. 1.53(b))

Expediente No.: 6577.US.01

Primer Inventor o Identificador de la Solicitud: Philip R. Kym

Título: VER 1 EN ADENDOS

ELEMENTOS DE LA SOLICITUD

Ver MPEP capítulo 800 sobre contenidos de la solicitud de patente utilitaria.

1. ☒ Formato de Transmisión de Derechos (es decir PTO/SB/17)
(presentar original y duplicado para procesamiento de derechos)
2. ☒ Especificaciones (Total de páginas 79)
(Distribución preferida según se indica a continuación)
 - Título descriptivo del invento
 - Referencias cruzadas con solicitudes relacionadas
 - Declaración sobre fomento a la investigación y desarrollo
 - Referencia a Apéndice de Microficha
 - Antecedentes del Invento
 - Breve Resumen del Invento
 - Breve Descripción de los Planos (si se presentan)
 - Descripción detallada
 - Reivindicaciones
 - Resumen del Invento
4. Juramento o Declaración [Total páginas: 4]

[Signature]
GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV. 29-82
MINISTERIO DE JUSTICIA

94 92

a. ☒ Recientemente otorgado (original o copia)

PARTES QUE ACOMPAÑAN LA SOLICITUD

12.x Declaración de Pequeña Empresa (MPEP 503) (Debe discriminarse específicamente)

17. DIRECCION PARA CORRESPONDENCIA

☒ Dirección de la Correspondencia

Nombre: STEVEN F. WEINSTOCK

Abbott Laboratories

Dirección: 100 Abbott Park Road

D-377 AP6D

Ciudad: Abbott Park Estado: IL Código: 60064-6050

Tel: (847)937-4395 Fax: (847) 938-2623

Nombre: Janelle D. Strobe

No. de Registro: 34.738

Firma: Firmado

Fecha: Septiembre 1, 1999


GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV. 29-82
MINISTERIO DE JUSTICIA

Expediente de Profesional No.: 6577.US.01

PATENTE

EN LA OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS

Asunto: Solicitud de: Philip Kym. et al.

Solicitud No.: (no asignada aun)

Grupo No.: (no asignado aun)

Presentado:

Examinado: (no asignado aun)

Para: ANTAGONISTAS GLUCOCORTICOIDRECEPTORES PARA TRATAMIENTOS
DE DIABETES

Casilla de Solicitud de Patente

Comisionado Asistente para Patentes

Washington, D.C. 20231

CERTIFICADO DE CORREO EXPRESO

Marbete de "Correo Expreso" No EE835508206US

Fecha de Depósito: 09/01/1999

Adjunto los siguientes documentos:

1. Transmisión de Solicitud de Patente de Utilidad (por duplicado)
2. Formato de Derechos de Transmisión PTO SB/17 (por duplicado)
3. Declaración y Poder Otorgados para Apoderado (por duplicado)
4. Especificación de la invención (79 páginas en total)
incluyendo:
 - Descripción de la invención (54 páginas)

[Signature]
GABRIEL RUEDA CENDERO
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV. 29-82
MINISTERIO DE JUSTICIA

96 94

- Reivindicaciones (24 páginas)
- Resumen (1 página)

5. Tarjeta para Recibo de Retorno

han sido depositadas en la Oficina de Correo Expreso del Servicio Postal de los Estados Unidos para el destinatario del servicio de acuerdo con 37 CFR 1.10, en la fecha indicada arriba, y va dirigido al Comisionado Asistente de Patentes, Washington, D.C. 20231.

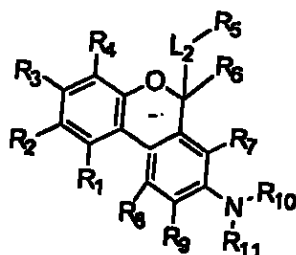
Janelle D. Strode

(Firmado)

Firma de la persona que remite los documento o derechos

96 94
GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
RESOLUCION 5996 DE NOV. 29-82
MINISTERIO DE JUSTICIA

1. Un compuesto de la formula I



I,

o una de sus sales o precursores de droga farmacéuticamente aceptables, donde:

R₁ es L₁-R_A.

R₂, R₃, R₄, R₇, R₈ y R₉ se seleccionan independientemente a partir de -L₁-R_A o H.

L₁ se selecciona a partir de:

- (1) un enlace covalente,
- (2) -O-,
- (3) -S(O)_t-, donde t es 0, 1, o 2,
- (4) -C(X)-, donde X es O o S,
- (5) -NR₁₂-, donde R₁₂ se selecciona a partir de
 - (a) hidrógeno,
 - (b) arilo,
 - (c) cicloalquilo C₁-C₁₂,
 - (d) alcanilo C₁-C₁₂,
 - (e) alcóxicarbonilo C₁-C₁₂,
 - (f) alcóxicarbonilo C₁-C₁₂ sustituido por 1 a 2 grupos de arilo,
 - (g) alquilo C₁-C₁₂,
 - (h) alquilo C₁-C₁₂ sustituido por 1 o 2 sustitutos seleccionados independientemente del arilo o cicloalquilo C₃-

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C₁₂.

(1) alquenilo C₃-C₁₂, siempre y cuando que un carbono del doble enlace carbono-carbono no se adhiera directamente al nitrógeno,

(2) alquinilo C₃-C₁₂, siempre y cuando que un carbono de triple enlace carbono-carbono no se adhiera directamente al nitrógeno.

(6) -NR₁₃C(X)NR₁₄- donde X es O o S y R₁₃ y R₁₄ se seleccionan independientemente a partir de

(a) hidrógeno,

(b) arilo,

(c) cicloalquilo C₃-C₁₂,

(d) alquilo C₁-C₁₂,

(e) alquilo C₁-C₁₂ sustituido por 1 o 2 sustitutos seleccionados independientemente a partir de arilo o cicloalquilo C₃-C₁₂,

(f) alquenilo C₃-C₁₂,

a condición de que un carbono de un doble enlace carbono-carbono no se adhiere directamente al nitrógeno,

(g) alquinilo C₃-C₁₂, a condición de que un carbono de un triple enlace carbono-carbono no se adhiere directamente al nitrógeno,

(7) -X'C(X)-, donde X corresponde a la definición dada anteriormente y X' es O o S,

(8) -C(X)X'-, donde X y X' corresponden a la definición dada anteriormente,

(9) -X'C(X)X"-, donde X y X' corresponden a la definición dada anteriormente, y X" es O o S, a condición de que cuando X sea O, por lo menos uno de los X' o X" sea O,

(10) -NR₁₃C(X)-,

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- (11) $-C(X)NR_{13}-$,
- (12) $-NR_{13}C(X)X'-$,
- (13) $-X'C(X)NR_{13}-$,
- (14) $-SO_2NR_{13}-$,
- (15) $-NR_{13}SO_2-$, y
- (16) $-NR_{13}SO_2NR_{14}-$.

donde (8) - (16) se retiran con sus extremos derechos adheridos a R_A ;

R_A se selecciona a partir de:

- (1) $-OH$,
- (2) $-OG$ donde G es un grupo protector $-OH$,
- (3) $-SH$,
- (4) $-CN$.
- (5) halo,
- (6) haloalcoxi de uno a doce carbonos,
- (7) perfluoroalcoxi de uno a doce carbonos,
- (8) $-CHO$,
- (9) $-NR_{12}R_{12}-$, donde R_7 se encuentra definido con anterioridad y $R_{12}-$ se selecciona a partir de
 - (a) hidrógeno,
 - (b) arilo,
 - (c) cicloalquilo C_3-C_{12} ,
 - (d) alcanilo C_1-C_{12} ,
 - (e) alcóxicarbonilo C_1-C_{12} ,
 - (f) alcóxicarbonilo C_1-C_{12} sustituido por 1 o 2 grupos arilo,
 - (g) alquilo C_1-C_{12} ,
 - (h) alquilo C_1-C_{12} sustituido por 1 o 2 sustitutos seleccionados independientemente del arilo o cicloalquilo C_3-

C₁₂.

(1) alqueno C₃-C₁₂, a condición de que un carbono de un doble enlace carbono-carbono no se adhiera directamente al nitrógeno,

(2) alquino C₃-C₁₂, a condición de que un carbono de un triple enlace carbono-carbono no se adhiera directamente al nitrógeno,

(10) -C(X)NR₁₃R₁₄,

(11) -OSO₂R₁₅ donde R₁₅ se selecciona a partir de

(a) arilo,

(b) cicloalquilo C₃-C₁₂,

(c) alquilo C₁-C₁₂,

(d) alquilo C₁-C₁₂ sustituido por 1, 2, 3 o 4 halo sustitutos, y

(e) perfluoroalquilo C₁-C₁₂, a condición de que cuando R_A sea (1) hasta (11), L₁ sea un enlace covalente.

(12) alquilo C₁-C₁₂,

(13) alqueno C₂-C₁₂, a condición de que un carbono de un doble enlace carbono-carbono no se adhiera directamente a L₁ cuando L₁ sea distinto de un enlace covalente,

(14) alquino C₂-C₁₂, a condición de que un carbono de un triple enlace carbono-carbono no se adhiera directamente a L₁ cuando L₁ sea distinto de un enlace covalente, donde (12), (13) y (14) se pueda sustituir opcionalmente por 1, 2 o 3 sustitutos seleccionados independientemente de

(a) alcoxi C₁-C₁₂.

(b) -OH, a condición de que ninguno de los dos grupos -OH se adhieran al mismo carbono,

(c) -SH, a condición de que ninguno de los dos grupos -SH se adhieran al mismo carbono,

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- (d) -CN,
- (e) halo,
- (f) -CHO,
- (g) -NO₂,
- (h) haloalcoxi C₁-C₁₂,
- (i) perfluoroalcoxi C₁-C₁₂,
- (j) -NR₁₂R₁₂⁻,
- (k) =NNR₁₂R₁₂⁻,

(l) -NR₁₂R₁₂-NR₁₂" donde R₁₂ y R₁₂⁻ corresponden a la definición dada anteriormente, R₁₂" se selecciona a partir de:

- (i) hidrógeno,
- (ii) arilo,
- (iii) cicloalquilo C₃-C₁₂,
- (iv) alcanoilo C₁-C₁₂,
- (v) alcoxycarbonilo C₁-C₁₂,
- (vi) alcoxycarbonilo C₁-C₁₂ sustituido por 1 o 2 grupos arilo,
- (vii) alquilo C₁-C₁₂,
- (viii) alquilo C₁-C₁₂ sustituido por 1 o 2 sustitutos seleccionados independientemente a partir de arilo o cicloalquilo C₃-C₁₂,
- (ix) alquenoilo C₃-C₁₂, a condición de que un doble enlace carbono-carbono no se adhiera directamente al nitrógeno,
- (x) alquinoilo C₃-C₁₂, a condición de que un triple enlace carbono-carbono no se adhiera directamente al nitrógeno,
- (m) -CO₂R₁₈ donde R₁₈ se selecciona a partir de:
 - (i) arilo,

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(ii) arilo sustituido por 1, 2, o 3 alquilo C₁-C₁₂,
(ii) cicloalquilo C₃-C₁₂,
(iii) alquilo C₁-C₁₂ y
(iv) alquilo C₁-C₁₂ sustituido por arilo o
cicloalquilo C₃-C₁₂,

(n) -C(X)NR₁₃R₁₄,

(o) =N-OR₁₅,

(p) =NR₁₅,

(q) -S(O)_tR₁₅,

(r) -X'C(X)R₁₅,

(s) (=X), y

(t) -OSO₂R₁₅,

(15) cicloalquilo C₃-C₁₂,

(16) cicloalquenilo C₄-C₁₂,

a condición de que un carbono de un doble enlace carbono-carbono no se adhiera directamente a L₁ cuando L₁ es distinto a un enlace covalente.

donde (15) y (16) pueden ser sustituidos opcionalmente por 1, 2, 3, o 4 sustitutos seleccionados independientemente de:

(a) alquilo C₁-C₁₂,

(b) arilo,

(c) alcoxi C₁-C₁₂,

(d) halo, y

(e) -OH, a condición de que ninguno de los dos grupos -OH se adhieran al mismo carbono,

(17) perfluoroalquilo C₁-C₁₂,

(18) arilo, y

(19) heterociclo

donde (18) y (19) pueden sustituirse opcionalmente por 1, 2, 3, 4, o 5 sustitutos seleccionados independientemente a

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partir de:

- (a) alquilo C_1-C_{12} ,
- (b) alcanoiloxi C_1-C_{12} ,
- (c) alcoxicarbonilo C_1-C_{12} ,
- (d) alcoxi C_1-C_{12} ,
- (e) halo,
- (f) $-OH$,

a condición de que ninguno de los dos grupos $-OH$ se adhieran al mismo carbono,

- (g) tioalcoxi C_1-C_{12} ,
- (h) perfluoroalquilo C_1-C_{12} ,
- (i) $-NR_{12}R_{12}-$,
- (j) $-CO_2R_{12}$,
- (k) $-OSO_2R_{12}$, y
- (l) $(=X)$; o

R_1 y R_2 conjuntamente son $-X^*-Y^*-Z^*-$ donde X^* es $-O-$ o $-CH_2-$, Y^* es $-C(O)-$ o $-(C(R_{17})(R_{18}))_v-$ donde R_{17} y R_{18} son independientemente hidrógeno o alquilo C_1-C_{12} y v es 1, 2, o 3, y Z^* se selecciona a partir de $-CH_2-$, $-CH_2S(O)_t-$, $-CH_2O-$, $-CH_2NR_{12}-$, $-NR_{12}-$, y $-O-$;

L_2 se selecciona a partir de

- (1) un enlace covalente,
- (2) alquilenos C_1-C_{12} ,
- (3) alquilenos C_1-C_{12} sustituido por 1 o 2 sustitutos seleccionados independientemente a partir de
 - (a) espiroalquilo C_3-C_6 ,
 - (b) espiroalquilenos C_3-C_6 ,
 - (c) oxo,

- (d) halo, y
- (e) -OH, a condición de que ninguno de los dos grupos -OH se adhieran al mismo carbono,
- (4) alquínileno C₁-C₁₂,
- (5) -NR₁₂-,
- (6) -C(X)-,
- (7) -O-, y
- (8) -S(O)_t-; y

R₅ se selecciona a partir de:

- (1) halo,
- (2) -C(=NR₁₂)OR₁₅,
- (3) -CN, a condición de que cuando R₅ sea (1), (2), o (3), L₂ sea un enlace covalente,
- (4) alquilo C₁-C₁₂,
- (5) alquínilo C₂-C₁₂, a condición de que un carbono de un triple enlace carbono-carbono no se adhiera directamente a L₃ cuando L₃ es distinto a un enlace covalente,
- (6) cicloalquilo C₃-C₁₂,
- (7) heterociclo,
- (8) arilo

donde (4) - (8) pueden sustituirse opcionalmente por 1, 2, 3, 4, o 5 sustitutos seleccionados independientemente a partir de

- (a) -OH, a condición de que ninguno de los dos grupos -OH se adhieran al mismo carbono,
- (b) -SH, a condición de que ninguno de los dos grupos -SH se adhieran al mismo carbono,
- (c) -CN,
- (d) halo,

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- (e) -CHO,
- (f) -NO₂,
- (g) haloalcoxi C₁-C₁₂,
- (h) perfluoroalcoxi C₁-C₁₂.
- (i) -NR₁₃-R₁₄-, donde R₁₃- y R₁₄- se seleccionan a partir de:

- (i) hidrógeno,
- (ii) alcanoilo C₁-C₁₂,
- (iii) alcoxycarbonilo C₁-C₁₂,
- (iv) alcoxycarbonilo C₁-C₁₂ sustituido por 1 a 2 sustitutos de fenilo,
- (v) cicloalquilo C₃-C₁₂,
- (vi) alquilo C₁-C₁₂,
- (vii) alquilo C₁-C₁₂ sustituido por 1, 2, o 3 sustitutos seleccionados independientemente de alcoxi C₁-C₁₂, cicloalquilo C₃-C₁₂, y arilo,

(viii) alquenilo C₃-C₁₂,
a condición de que un carbono de un doble enlace carbono-carbono no se adhiera directamente al nitrógeno,

(ix) alquinilo C₃-C₁₂.
a condición de que un carbono de un triple enlace carbono-carbono no se adhiera directamente al nitrógeno,

- (x) arilo,
- (xi) arilo sustituido por 1, 2, 3, 4, o 5 sustitutos seleccionados independientemente a partir de alquilo C₁-C₁₂, alcanoiloxi C₁-C₁₀, alcoxycarbonilo C₁-C₁₂, alcoxi C₁-C₁₂, halo, -OH, a condición de que ninguno de los dos grupos -OH se adhieran al mismo carbono, tioalcoxi de uno a doce carbonos, perfluoroalquilo de uno a doce carbonos, -NR₁₂R₁₂-, -CO₂R₁₅, -OSO₂R₁₅, y (=X), o

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R₁₃ y R₁₄ conjuntamente con el átomo de nitrógeno al cual se adhieren forman un anillo seleccionado a partir de

- (i) aziridina,
- (ii) azetidina,
- (iii) pirrolidina,
- (iv) piperidina,
- (v) pirazina,
- (vi) morfolina,
- (vii) triomorfolina, y
- (viii) sulfona de tiomorfolina

donde (i) - (viii) pueden sustituirse opcionalmente por 1, 2, o 3 alquilo C₁-C₁₂.

- (j) =NR₁₃-R₁₄,
- (k) -NR₁₂NR₁₃-R₁₄,
- (l) -CO₂R₁₃,
- (m) -C(X)NR₁₃-R₁₄,
- (n) =N-OR₁₃,
- (o) =NR₁₃,
- (p) -S(O)_tR₁₃,
- (q) -X'C(X)R₁₃,
- (r) (=X),

(s) -O-(CH₂)_q-Z-R₁₃ donde R₁₃ corresponde a la definición dada previamente, q es 1, 2, o 3, y Z es O o -S(O)_t,

- (t) -OC(X)NR₁₃-R₁₄,
- (u) -OSO₂R₁₃,
- (v) alcanoiloxi C₁-C₁₂,
- (w) -L₃R₃₀ donde L₃ se selecciona a partir de:
 - (i) un enlace covalente,
 - (ii) -O-

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(iii) $-S(O)_2-$, y

(iv) $-C(X)-$ y

Reso se selecciona a partir de

(i) alquilo C_1-C_{12} ,

(ii) alquenilo C_1-C_{12} ,

a condición de que un carbono de un doble enlace carbono-carbono no se adhiera directamente a L_2 cuando L_2 sea distinto a un enlace covalente,

(iii) alquinilo C_1-C_{12} , a condición de que un carbono de un triple enlace carbono-carbono no se adhiera directamente a L_2 cuando L_2 sea distinto a un enlace covalente, donde (i), (ii), y (iii) puede sustituirse opcionalmente por cicloalquilo C_3-C_{12} , $-OH$, a condición de que ninguno de los dos grupos $-OH$ se adhieran al mismo carbono, arilo y heterociclo,

(iv) arilo,

(v) arilo sustituido por 1, 2, 3, 4, o 5 sustitutos seleccionados independientemente a partir de alquilo C_1-C_{12} , halo, $-NO_2$, y $-OH$, a condición de que ninguno de los dos grupos $-OH$ se adhieran al mismo carbono,

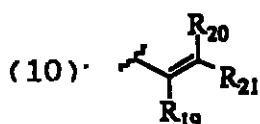
(vi) heterociclo, y

(vii) heterociclo sustituido por 1, 2, 3, 4, o 5 sustitutos seleccionados independientemente a partir de alquilo C_1-C_{12} , halo, $-NO_2$, y $-OH$, a condición de que ninguno de los dos grupos $-OH$ se adhieran al mismo carbono,

(x) $-X^*C(X)X''R_{15}$,

(y) $-C(=NR_7)OR_{15}$, y

(z) $-NR_7(X)NR_{13}-NR_{14}-$.



a condición de que cuando R_3 sea (9), L_3 sea distinto de -
NR₁₂- o -O-.

donde el doble enlace carbono-carbono se encuentra en la
configuración Z o E, y

R₁₉, R₂₀, y R₂₁ son seleccionados independientemente a partir
de

- (a) hidrógeno,
- (b) halo,
- (c) alquilo C₁-C₁₂, y
- (d) alquilo C₁-C₁₂ sustituido por
 - (i) alcoxi C₁-C₁₂.
 - (ii) -OH, a condición de que ninguno de los dos
grupos -OH se adhieran al mismo carbono,
 - (iii) -SH, a condición de que ninguno de los
dos grupos -SH se adhieran al mismo carbono,
 - (iv) -CN,
 - (v) halo,
 - (vi) -CHO,
 - (vii) -NO₂,
 - (viii) haloalcoxi C₁-C₁₂,
 - (ix) perfluoroalcoxi C₁-C₁₂,
 - (x) -NR₁₃-R₁₄,
 - (xi) =NNR₁₃-R₁₄,
 - (xii) -NR₁₂NR₁₃-R₁₄,
 - (xiii) -CO₂R₁₅,
 - (xiv) -C(X)NR₁₃-R₁₄,
 - (xv) =N-OR₁₅,

- (xvi) $=NR_{15}$.
- (xvii) $-S(O)_tR_{15}$.
- (xviii) $-X^*C(X)R_{15}$.
- (xix) $(=X)$.
- (xx) $-O-(CH_2)_q-Z-R_{15}$.
- (xxi) $-OC(X)NR_{13}-R_{14}$.
- (xxii) $-LsR_{30}$.
- (xxiii) alcanoiilo C_1-C_{12} .
- (xxiv) $-OSO_2R_{15}$, y
- (xxv) $-NR_7(X)NR_{13}-R_{14}$, o

R₂₀ y R₂₁ conjuntamente se seleccionan de

- (a) cicloalquilo C_3-C_{12} .
- (b) cicloalqueno C_4-C_{12} , y

- (c) $\begin{array}{c} R_{22} \\ \diagup \\ = \\ \diagdown \\ R_{23} \end{array}$ (aleno) donde R₂₂ y R₂₃ son

independientemente hidrógeno o alquilo C_1-C_{12} , y

(10) carbonos de cicloalqueno C_4-C_{12} donde el grupo cicloalqueno o el anillo formado por R₂₀ y R₂₁ conjuntamente pueden ser sustituidos opcionalmente por uno o dos sustitutos que se seleccionan independientemente de

- (a) alcoxi C_1-C_{12} .
- (b) $-OH$, a condición de que ninguno de los dos grupos $-OH$ se adhieran al mismo carbono,
- (c) $-SH$, a condición de que ninguno de los dos grupos $-SH$ se adhieran al mismo carbono,
- (d) $-CN$.
- (e) halo,
- (f) $-CHO$,

- (g) $-\text{NO}_2$.
- (h) haloalcoxi C1-C12,
- (i) perfluoroalcoxi C1-C12,
- (j) $-\text{NR}_{13}-\text{R}_{14}$.
- (k) $=\text{NNR}_{13}-\text{R}_{14}$.
- (l) $-\text{NR}_{12}\text{NR}_{13}-\text{R}_{14}$.
- (m) $-\text{CO}_2\text{R}_{15}$,
- (n) $-\text{C}(\text{X})\text{NR}_{13}\text{R}_{14}$.
- (o) $=\text{N}-\text{OR}_{15}$,
- (p) $=\text{NR}_{15}$,
- (q) $-\text{S}(\text{O})_t\text{R}_{15}$,
- (r) $-\text{X}-\text{C}(\text{X})\text{R}_{15}$,
- (s) $(=\text{X})$,
- (t) $-\text{O}-(\text{CH}_2)_q-\text{Z}-\text{R}_{15}$,
- (u) $-\text{OC}(\text{X})\text{NR}_{13}-\text{R}_{14}$,
- (w) alcanoiloxi C1-C12,
- (x) $-\text{OSO}_2\text{R}_{15}$, y
- (y) $-\text{NR}_7(\text{X})\text{NR}_{13}-\text{R}_{14}$:

R_8 es hidrógeno o alquilo C1-C12; o

$-\text{L}_2-\text{R}_8$ y R_8 conjuntamente son



donde d es 1, 2, 3, o 4 y A se selecciona de:

- (a) $-\text{CH}_2-$.
- (b) $-\text{O}-$,
- (c) $-\text{S}(\text{O})_t$, y
- (d) $-\text{NR}_{12}-$, o

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(2) $\begin{array}{c} R_{26} \\ \diagup \\ \text{C} \\ \diagdown \\ H \end{array}$ donde el doble enlace carbono-carbono puede estar en la configuración E o Z y R₂₆ se selecciona de

- (a) arilo.
- (b) heterociclo.
- (c) alquilo C₁-C₁₂.
- (d) cicloalquilo C₃-C₁₂.
- (e) cicloalquenilo C₄-C₁₂, y
- (f) cicloalquenilo C₄-C₁₂ donde (a) - (f) puede sustituirse opcionalmente por 1, 2, 3, 4, o 5 sustitutos seleccionados independientemente a partir de:

- (i) alcoxi C₁-C₁₂,
- (ii) -OH, a condición de que ninguno de los dos grupos -OH se adhieran al mismo carbono,
- (iii) -SH, a condición de que ninguno de los dos grupos -SH se adhieran al mismo carbono,
- (iv) -CN.
- (v) halo,
- (vi) -CHO.
- (vii) -NO₂,
- (viii) haloalcoxi C₁-C₁₂.
- (ix) perfluoroalcoxi C₁-C₁₂,
- (x) -NR₁₃-R₁₄⁻,
- (xi) =NNR₁₃-R₁₄⁻,
- (xii) -NR₁₂NR₁₃-R₁₄⁻,
- (xiii) -CO₂R₁₅,
- (xiv) -C(X)NR₁₃-R₁₄⁻,
- (xv) =N-OR₁₅,
- (xvi) =NR₁₅,
- (xvii) -S(O)_tR₁₅,
- (xviii) -X'C(X)R₁₅,

- (xix) (=X),
- (xx) -O-(CH₂)_q-Z-R₁₅,
- (xxi) -L₂R₃₀,
- (xxii) alcanoiloxi C₁-C₁₂,
- (xxiii) -OSO₂R₁₅, y
- (xxiv) -NR₁₂(X)NR₁₃-R₁₄;

R₁₀ y R₁₁ se seleccionan independientemente a partir de

- (i) hidrógeno,
 - (ii) alcanilo C₁-C₁₂;
 - (iii) alcoxicarbonilo C₁-C₁₂;
 - (iv) alcoxicarbonilo C₁-C₁₂ y se sustituye por 1 o 2 sustitutos de fenilo,
 - (v) cicloalquilo C₁-C₁₂,
 - (vi) alquilo C₁-C₁₂,
 - (vii) alquilo C₁-C₁₂ sustituido por 1, 2, o 3 sustitutos seleccionados independientemente a partir de alcoxi C₁-C₁₂, cicloalquilo C₃-C₁₂, y arilo,
 - (viii) alqueno C₃-C₁₂,
- a condición de que un carbono de un doble enlace carbono-carbono no se adhiera directamente al nitrógeno,
- (ix) alquino C₃-C₁₂
- a condición de que un carbono de un triple enlace carbono-carbono no se adhiera directamente al nitrógeno,
- (x) arilo,
 - (xi) arilo sustituido por 1, 2, 3, 4, o 5, sustitutos seleccionados independientemente de alquilo C₁-C₁₂, alcanoiloxi C₁-C₁₂, alcoxicarbonilo C₁-C₁₂, alcoxi C₁-C₁₂, halo, -OH, a condición de que ninguno de los dos grupos -OH se adhieran al mismo carbono, tioalcoxi C₁-C₁₂,

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perfluoroalquilo C1-C12, -NR₁₂R₁₂-,

-CO₂R₁₈.

-OSO₂R₁₈, y

(=X).

(xii) -S(O)_tR₁₈, donde t es 0, 1, o 2, y R₁₈ se selecciona de

(1) alquilo C1-C12,

(2) alqueno C2-C12,

(3) alquino C2-C12 donde (1) - (3) puede sustituirse opcionalmente,

(4) -OH, y

(5) -NR₁₂R₁₂-;

R₁₀ y R₁₁ conjuntamente con el átomo de nitrógeno al cual se adhieren forman un anillo seleccionado a partir de

(i) aziridina,

(ii) azetidina,

(iii) pirrolidina,

(iv) piperidina,

(v) pirazina,

(vi) morfolina,

(vii) triomorfolina, y

(viii) sulfona de tiomorfolina

donde (i) - (viii) pueden sustituirse opcionalmente por 1, 2, o 3 alquilo C1-C12, o

R₁₀ y R₇ conjuntamente con el anillo al cual se adhieren forman un anillo de 5-, 6-, o 7- miembros con 0, 1, o 2 dobles enlaces y 0-4 sustitutos que se seleccionan a partir de un grupo conformado por alquilo, halógeno u oxo; y

HA
C12

R₆ y R₇ conjuntamente con el anillo al cual se adhieren forman un anillo de 5-, 6-, o 7- miembros con 0, 1, o 2 dobles enlaces y 0-4 sustitutos que se seleccionan a partir de un grupo conformado por alquilo C₁-C₁₂, halógeno u oxo.

2. Un compuesto de acuerdo con la reivindicación 1 donde

R₁ es -L₁-L_A donde

L₁ se selecciona de

- (1) un enlace covalente,
- (2) -O-,
- (3) -C(X)X'- donde X y X' son O,
- (4) -X'C(X)- donde X y X' son O, y
- (5) -X'C(X)X"- donde X y X', y X" son O y

R_A se selecciona de

- (1) alquilo de uno a doce carbonos,
- (2) alquenilo de dos a doce carbonos,
- (3) alquinilo de dos a doce carbonos donde (1) - (3) pueden estar sustituidos opcionalmente,
- (4) -OH, y
- (5) -NR₁₂R₁₂-.

R₂ es hidrógeno o -L₁-R_A donde L₁ es -O- y R_A es alquilo de uno a doce carbonos;

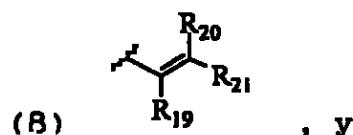
R₃, R₄, R₅, y R₆ son hidrógeno,

L₂ es un enlace covalente o -NR₁₂-;

R₅ se selecciona de

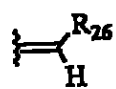
- (1) halo,
- (2) -C(=NR₇)OR₁₀,
- (3) -CN,

- (4) alquilo de uno a doce carbonos,
- (5) alquinilo de dos a doce carbonos,
- (6) heterociclo,
- (7) arilo.



- (9) cicloalquenilo de cuatro a doce carbonos
- donde (4) - (7), (9), y los sustitutos definidos por R19, R20, y R21 en (8) pueden estar sustituidos opcionalmente; y

R8 es hidrógeno; o

-L2-R8 y R8 conjuntamente son  donde los sustitutos definidos por R26 pueden estar opcionalmente sustituidos.

R7 es hidrógeno; o R7 y R10 conjuntamente con el anillo al cual se adhieren forman un anillo de 5-, 6-, o 7-miembros con 1-2 dobles enlaces y 0-4 sustitutos seleccionados a partir de un grupo consistente en alquilo, halógeno u oxo.

R10 y R11 se seleccionan independientemente a partir del hidrógeno; -C(O)R35, o -S(O)tR35, donde t es 0, 1, o 2, y R35 se selecciona de:

- (1) alquilo de uno a doce carbonos,
- (2) alquenilo de dos a doce carbonos,
- (3) alquinilo de dos a doce carbonos donde (1) - (3) pueden estar sustituidos opcionalmente,

- (4) $-OR_{15}$, y
(5) $-NR_{12}R_{12}$; o

3. Un compuesto de acuerdo con la reivindicación 2 donde L_1 es O y R_A es alquilo de uno a doce carbonos que se pueden sustituir opcionalmente.

4. Un compuesto de acuerdo con la reivindicación 3 donde R^{10} se selecciona a partir de $S(O)_tR_{35}$, donde t es 0, 1, o 2, y R^{35} se selecciona a partir de alquilo de uno a cuatro carbonos.

5. Un compuesto de acuerdo con la reivindicación 4 que se selecciona a partir de:

N-[1-metoxi-7-metil-6-[3-(trifluorometil)fenil]-6H-dibenzo-
[b,d]piran-6-11]metanosulfonamida;

N-(7-bromo-1-metoxi-6-fenil-6H-dibenzo[b,d]piran-6-
11]metanosulfonamida;

N-[7-bromo-1-metoxi-6-[3-(trifluorometil)fenil]-6H-dibenzo-
[b,d]piran-6-11]metanosulfonamida;

N-[1-metoxi-7-(1-metileténilo)-6-[3-(trifluorometil)fenil]-
6H-dibenzo[b,d]piran-6-11]metanosulfonamida;

N-[7-etenil-1-metoxi-6-[3-(trifluorometil)fenil]-6H-dibenzo-
[b,d]piran-6-11]metanosulfonamida; y

N-[7-bromo-1-metoxi-6-(3,5-dimetilfenil)-6H-dibenzo[b,d]-
piran-6-11]metanosulfonamida.

6. Un método de modulación selectiva de los efectos antagonistas del receptor glucocorticoide en un mamífero que comprende la administración de una cantidad eficaz de un

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compuesto de la reivindicación 1.

7. Un método para el tratamiento de la diabetes en un mamífero que comprende la administración de una cantidad eficaz de un compuesto de la reivindicación 1.

8. Un método para el tratamiento de la diabetes en un mamífero que comprende la administración de una cantidad eficaz de un antagonista receptor del glucocorticoide.

9. Un método de acuerdo con la reivindicación 8, donde el mencionado antagonista receptor del glucocorticoide se administra en ausencia de un agonista receptor del glucocorticoide.

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Santafé de Bogotá D.C., Septiembre 7 del 2000.

huc
GABRIEL RUEDA CHADID
TRADUCTOR OFICIAL
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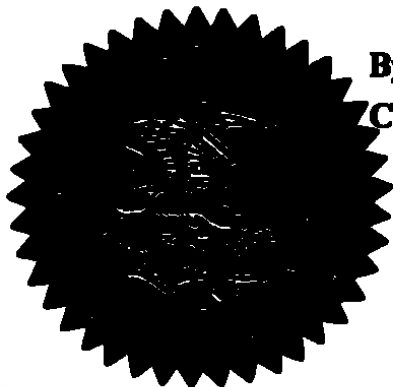
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APPLICATION NUMBER: 09/388,251

FILING DATE: September 01, 1999



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UTILITY PATENT APPLICATION TRANSMITTAL

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Attorney Docket No. **6577.US.01**

First Inventor or Application Identifier **Philip R. Kym**

Title **See 1 in Addendum**

Express Mail Label No. **EB835508206US**

APPLICATION ELEMENTS

See MPEP chapter 900 concerning utility patent application contents.

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- ☒ Fee Transmittal Form (e.g., PTO/SB/17)
(Submit an original and a duplicate for fee processing)
- ☒ Specification (Total Pages **79**)
(preferred arrangement set forth below)
 - Descriptive title of the invention
 - Cross References to Related Applications
 - Statement Regarding Fed sponsored R & D
 - Reference to Microfiche Appendix
 - Background of the invention
 - Brief Summary of the invention
 - Brief Description of the Drawings (if filed)
 - Detailed Description
 - Claim(s)
 - Abstract of the Disclosure
- ☐ Drawing(s) (35 U.S.C. 113) (Total Sheets ☐)
- oath or Declaration (Total Pages **4**)
 - ☒ Newly executed (original or copy)
 - ☐ Copy from a prior application (37 C.F.R. § 1.63(d))
(for continuation/divisional with Box 16 completed)
 - ☐ DELETION OF INVENTOR(S)
Signed statement attached deleting
inventor(s) named in the prior application,
see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

- ☐ Microfiche Computer Program (Appendix)
- Nucleotide and/or Amino Acid Sequence Submission
(if applicable, all necessary)
 - ☐ Computer Readable Copy
 - ☐ Paper Copy (identical to computer copy)
 - ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

- ☐ Assignment Papers (cover sheet & document(s))
- ☐ 37 C.F.R. § 3.73(b) Statement of Power of Attorney
(when there is an assignee)
- ☐ English Translation Document (if applicable)
- ☐ Information Disclosure Statement (IDS) PTO-1449 ☐ Copies of IDS Citations
- ☐ Preliminary Amendment
- ☒ Return Receipt Postcard (MPEP 503)
(Should be specifically formatted)
 - * Small Entity Statement filed in prior application
(PTO/SB-08-12) Status still proper and desired
- ☐ Certified Copy of Priority Document(s)
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	D-377 AP6D	
City	Abbott Park	State IL Zip Code 60064-6050
Country	Telephone (847) 937-4395	Fax (847) 938-2623

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Philip Kym, *et al.*

Application No.: (not yet assigned)

Group No.: (not yet assigned)

Filed:

Examiner: (not yet assigned)

For: GLUCOCORTICOIDRECEPTORANTAGONISTS FOR TREATMENT OF DIABETES

Box Patent Application

Assistant Commissioner for Patents

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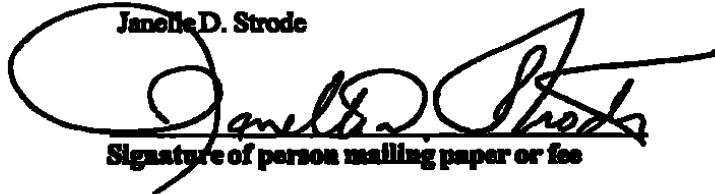
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I hereby state that the following *attached* papers

1. Utility Patent Application Transmittal (in duplicate)
2. Fee Transmittal Form PTO SB/17 (in duplicate)
3. Executed, Declaration and Power of Attorney (in duplicate)
4. Invention specification (79 pages total) including:
 - Description of invention (54 pages)
 - Claims (24 pages)
 - Abstract (1 page)
5. Return Receipt Postcard

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GLUCOCORTICOID RECEPTOR ANTAGONISTS
FOR TREATMENT OF DIABETES

Technical Field

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5 The present invention relates to glucocorticoid
receptor-selective antagonists that are useful for treating
diabetes.

Background of the Invention

15 Type II diabetes (also referred to as non insulin-
dependent Diabetes Mellitus) is a debilitating disease
characterized by an abnormal elevation of blood glucose
levels driven by three factors: increased hepatic glucose
production, inadequate clearance of glucose via insulin
mediated pathways, and decreased uptake of circulating
glucose by tissues. (DeFronzo, *Diabetes Review* 5(3), 177-
269, (1997)). Administration of agents that decrease
hepatic glucose production are a fundamental approach to
controlling blood glucose. (De Foa et al., *Am. J. Physiol.*

257, E35-E42 (1989); Rooney, et al., *J. Clin. Endocrinol. Metab.* 77, 1180-1183 (1994); Dinneen et al., *J. Clin. Invest.*, 92, 2283-2290 (1993)). Glucocorticoids have been shown to have major influences on glucose production.

- 5 Glucocorticoid excess aggravates established diabetes while glucocorticoid deficiency reduces blood glucose and improves glucose control in diabetic mice. (Boyle, *Diabetes Review*, 1(3), 301-308, (1993); Naeser, *Diabetologia*, 9, 376-379 (1973); Solomon et al., *Horm. Metab. Res.*, 9, 152-156 (1977)).
- 10

The underlying mechanism responsible for these effects is the glucocorticoid-induced upregulation of key hepatic enzymes required for gluconeogenesis. (Exton et al., *Recent Prog. Horm. Res.*, 26, 411-457 (1970); Kraus-

15 Friedmann, *Physiol. Rev.*, 64, 170-259 (1984).

Pharmaceutical agents that function as glucocorticoid receptor (GR) antagonists represent a novel approach to controlling type II diabetes.

- The glucocorticoids are lipid soluble hormones
- 20 synthesized in the adrenal cortex. (Neville and O'Hare, The Adrenal Gland, James, Ed. New York, Raven, 1-65, (1979).

- These molecules readily pass through cell membranes and enter the cytoplasm of target tissues, where they bind to glucocorticoid receptors sequestered in the cytoplasm by
- 25 complexation with heat shock proteins. Upon binding of the

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hormone to its receptor, the receptor undergoes a conformational change which results in dissociation of heat shock proteins, and translocation of the ligand bound glucocorticoid receptor into the nucleus where it can either
5 initiate or repress specific gene transcription.

Transcriptional activation occurs when the ligand bound receptor complex homodimerizes, and the homodimeric receptor ligand complex binds to chromosomal DNA at sequence specific sites in the promoter region of regulated genes. (Beato,
10 Cell, 56, 335-344 (1989); Yamamoto, Annu. Rev. Genet., 19, 209-215 (1989)). Among the genes that glucocorticoids up-regulate are several genes that play key roles in gluconeogenesis and glycogenolysis, particularly PEPCK and glucose-6-phosphatase. (Hanson and Patel, Adv. Enzymol.,
15 Meister, Ed. New York, John Wiley and Sons, Inc., 203-281 (1994); Argaud et al., Diabetes 45, 1563-1571 (1996)).

PEPCK catalyzes the conversion of oxaloacetate to phosphoenolpyruvate and glucose-6-phosphatase catalyzes the conversion of glucose-6-phosphate into glucose, both of
20 these transformations are required for the synthesis of glucose from oxaloacetate in the liver. Recently, it has been shown that mifepristone (RU486), a potent GR antagonist reduces mRNA levels of PEPCK and glucose-6-phosphate in the liver, and causes a 50% reduction of plasma glucose levels
25 in obese diabetic db/db transgenic mice. (Friedman et al., J. Biol. Chem. 272(50), 31475-31481 (1997)). While steroid-

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based GR antagonists have been useful in demonstrating efficacy for in vivo glucose lowering effects, the utility of such agents is limited due to side effects resulting from potent cross-reactivity with other steroid receptors, in particular progesterone receptor (PR) and mineralocorticoid receptor (MR).

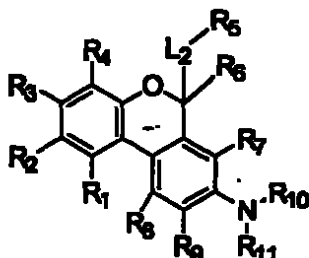
US 5,929,058 discloses a method for treating type II diabetes by administering a combination of steroidal-agents that exhibit mineralocorticoid receptor agonist activity and glucocorticoid receptor antagonist activity. BE 890773 discloses a group of dibenzo(b,d)pyran derivatives useful for gastrointestinal ulcers, autoimmune diseases, and viral and bacterial infections. BE 823873 discloses a group of dibenzo(b,d)pyran derivatives used as anxiolytic, antidepressive, and-antipsychotic agents.

Thus, it would be an important contribution to the art to provide compounds which are glucocorticoid selective non-steroidal agents that antagonize functional activity mediated by the glucocorticoid receptor, and which are useful for treating mammals suffering from type II diabetes, and for treating symptoms of type II diabetes, including hyperglycemia, inadequate glucose clearance, obesity, hyperinsulinemia, hypertriglyceridemia, high circulating glucocorticoid levels, and the like.

Summary of the Invention

The present invention relates to compounds of formula I

5



I

10 or a pharmaceutically acceptable salt or prodrug thereof,
wherein:

R₁ is L₁-R_A,

R₂, R₃, R₄, R₇, R₈, and R₉ are independently selected
from -L₁-R_A or H,

15 L₁ is selected from:

- (1) a covalent bond,
- (2) -O-,
- (3) -S(O)_t-, where t is 0, 1, or 2,
- (4) -C(X)-, where X is O or S,
- 20 (5) -NR₁₂-, where R₁₂ is selected from
 - (a) hydrogen,
 - (b) aryl,
 - (c) C₁-C₁₂ cycloalkyl,
 - (d) C₁-C₁₂ alkanoyl,
 - 25 (e) C₁-C₁₂ alkoxy carbonyl,

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(f) C₁-C₁₂ alkoxy carbonyl substituted with 1 to 2 aryl groups,

(g) C₁-C₁₂ alkyl,

(h) C₁-C₁₂ alkyl substituted with 1 or 2 substituents independently selected from aryl or C₃-C₁₂ cycloalkyl,

(i) C₁-C₁₂ alkenyl, provided that a carbon of a carbon-carbon double bond is not attached directly to nitrogen,

(j) C₃-C₁₂ alkynyl, provided that a carbon of a carbon-carbon triple bond is not attached directly to nitrogen,

(5) -NR₁₃C(X)NR₁₄- where X is O or S and R₁₃ and R₁₄ are independently selected from

(a) hydrogen,

(b) aryl,

(c) C₃-C₁₂ cycloalkyl,

(d) C₁-C₁₂ alkyl,

(e) C₁-C₁₂ alkyl substituted with 1 or 2

substituents independently selected from aryl or C₃-C₁₂ cycloalkyl,

(f) C₁-C₁₂ alkenyl,

provided that a carbon of a carbon-carbon double bond is not attached directly to nitrogen,

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(g) C_3-C_{12} alkynyl, provided that a carbon of a carbon-carbon triple bond is not attached directly to nitrogen,

(7) $-X'C(X)-$, wherein X is as previously defined
5 and X' is O or S,

(8) $-C(X)X'-$, wherein X and X' are as previously defined,

(9) $-X'C(X)X''-$, wherein X and X' are as previously defined, and X'' is O or S, provided that when X
10 is O, at least one of X' or X'' is O,

(10) $-NR_{13}C(X)-$,

(11) $-C(X)NR_{13}-$,

(12) $-NR_{13}C(X)X'-$,

(13) $-X'C(X)NR_{13}-$,

15 (14) $-SO_2NR_{13}-$,

(15) $-NR_{13}SO_2-$, and

(16) $-NR_{13}SO_2NR_{14}-$,

wherein (6)-(16) are drawn with their right ends attached to R_A ;

20 R_A is selected from

(1) $-OH$,

(2) $-OG$ where G is a $-OH$ protecting group,

(3) $-SH$,

(4) $-CN$,

25 (5) halo,

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- (6) haloalkoxy of one to twelve carbons,
- (7) perfluoroalkoxy of one to twelve carbons,
- (8) -CHO,
- (9) -NR₁₂R₁₂' where R₇ is defined previously and

5 R₁₂' is selected from

- (a) hydrogen,
- (b) aryl,
- (c) C₁-C₁₂ cycloalkyl,
- (d) C₁-C₁₂ alkanoyl,
- (e) C₁-C₁₂ alkoxy carbonyl,
- (f) C₁-C₁₂ alkoxy carbonyl substituted with 1

10 or 2 aryl groups,

- (g) C₁-C₁₂ alkyl,
- (h) C₁-C₁₂ alkyl substituted with 1 or 2

15 substituents independently selected from aryl or C₁-C₁₂ cycloalkyl,

(i) C₁-C₁₂ alkenyl, provided that a carbon of a carbon-carbon double bond is not attached directly to nitrogen,

20 (j) C₁-C₁₂ alkynyl, provided that a carbon of a carbon-carbon triple bond is not attached directly to nitrogen,

(10) -C(X)NR₁₃R₁₄,

(11) -OSO₂R₁₅ where R₁₅ is selected from

- 25
- (a) aryl,
 - (b) C₁-C₁₂ cycloalkyl,

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- (c) C_1-C_{12} alkyl,
- (d) C_1-C_{12} alkyl substituted with 1, 2, 3, or 4 halo substituents, and
- (e) C_1-C_{12} perfluoroalkyl, provided that when
- 5 R_A is (1) to (11), L_1 is a covalent bond,
- (12) C_1-C_{12} alkyl, --
- (13) C_2-C_{12} alkenyl, provided that a carbon of a carbon-carbon double bond is not attached directly to L_1 when L_1 is other than a covalent bond,
- 10 (14) C_2-C_{12} alkynyl, provided that a carbon of a carbon-carbon triple bond is not attached directly to L_1 when L_1 is other than a covalent bond, where (12), (13), and (14) can be optionally substituted with 1, 2, or 3 substituents independently selected from
- 15 (a) C_1-C_{12} alkoxy,
- (b) -OH, provided that no two -OH groups are attached to the same carbon,
- (c) -SH, provided that no two -SH groups are attached to the same carbon,
- 20 (d) -CN,
- (e) halo,
- (f) -CHO,
- (g) -NO₂,
- (h) C_1-C_{12} haloalkoxy,
- 25 (i) C_1-C_{12} perfluoroalkoxy, ...

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10 .

(j) $-NR_{12}R_{12}'$,(k) $-NNR_{12}R_{12}'$,

(l) $-NR_{12}NR_{12}'R_{12}''$ where R_{12} and R_{12}' are as previously defined and R_{12}'' is selected from

5 (i) hydrogen,

(ii) aryl,

(iii) C_3-C_{12} cycloalkyl,(iv) C_1-C_{12} alkanoyl,(v) C_1-C_{12} alkoxycarbonyl,10 (vi) C_1-C_{12} alkoxycarbonyl substituted

with 1 or 2 aryl groups,

(vii) C_1-C_{12} alkyl,

(viii) C_1-C_{12} alkyl substituted with 1 or
2 substituents independently selected from aryl or C_3-C_{12}
15 cycloalkyl,

(ix) C_3-C_{12} alkenyl, provided that a
carbon-carbon double bond is not attached directly to
nitrogen, and

(x) C_3-C_{12} alkynyl, provided that a
20 carbon-carbon triple bond is not attached directly to
nitrogen,

(m) $-CO_2R_{16}$ where R_{16} is selected from

(i) aryl,

(ii) aryl substituted with 1, 2, or 3

25 C_1-C_{12} alkyl,(ii) C_3-C_{12} cycloalkyl,09388251-090199
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(iii) C_1-C_{12} alkyl, and(iv) C_1-C_{12} alkyl substituted with aryl or C_3-C_{12} cycloalkyl,(n) $-C(X)NR_{13}R_{14}$,5 (o) $=N-OR_{16}$,(p) $=NR_{16}$,(q) $-S(O)_tR_{16}$,(r) $-X'C(X)R_{16}$,(s) $(=X)$, and10 (t) $-OSO_2R_{16}$,(15) C_3-C_{12} cycloalkyl,(16) C_4-C_{12} cycloalkenyl,

provided that a carbon of a carbon-carbon double bond is not attached directly to L_1 when L_1 is other than a covalent bond,

15 where (15) and (16) can be optionally substituted with 1, 2, 3, or 4 substituents independently selected from

(a) C_1-C_{12} alkyl,

(b) aryl,

20 (c) C_1-C_{12} alkoxy,

(d) halo, and

(e) $-OH$, provided that no two $-OH$ groups are attached to the same carbon,

(17) C_1-C_{12} perfluoroalkyl,

25 (18) aryl, and

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(19) heterocycle

where (18) and (19) can be optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from

- 5
- (a) C_1-C_{12} alkyl,
 - (b) C_1-C_{12} alkanoyloxy,
 - (c) C_1-C_{12} alkoxy carbonyl,
 - (d) C_1-C_{12} alkoxy,
 - (e) halo,
 - (f) $-OH$,

10 provided that no two $-OH$ groups are attached to the same carbon,

- 15
- (g) C_1-C_{12} thioalkoxy,
 - (h) C_1-C_{12} perfluoroalkyl,
 - (i) $-NR_{12}R_{12}'$,
 - (j) $-CO_2R_{16}$,
 - (k) $-OSO_2R_{16}$, and
 - (l) $(=X)$; or

20 R_1 and R_2 together are $-X^*-Y^*-Z^*-$ where X^* is $-O-$ or $-CH_2-$, Y^* is $-C(O)-$ or $-(C(R_{17})(R_{18}))_v-$ where R_{17} and R_{18} are independently hydrogen or C_1-C_{12} alkyl and v is 1, 2, or 3, and Z^* is selected from $-CH_2-$, $-CH_2S(O)_t-$, $-CH_2O-$, $-CH_2NR_{12}-$, $-NR_{12}-$, and $-O-$;

25 L_2 is selected from -----

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- (1) a covalent bond,
- (2) C_1-C_{12} alkylene,
- (3) C_1-C_{12} alkylene substituted with 1 or 2

substituents independently selected from

- 5 (a) C_3-C_6 spiroalkyl,
- (b) C_3-C_6 spiralkenyl,
- (c) oxo,
- (d) halo, and
- (e) -OH, provided that no two -OH groups are
- 10 attached to the same carbon,
- (4) C_1-C_{12} alkynylene,
- (5) $-NR_{12}-$,
- (6) $-C(X)-$,
- (7) $-O-$, and
- 15 (8) $-S(O)_t-$; and

 R_5 is selected from

- (1) halo,
- (2) $-C(=NR_{12})OR_{15}$,
- 20 (3) $-CN$, provided that when R_5 is (1), (2), or
- (3), L_2 is a covalent bond,
- (4) C_1-C_{12} alkyl,
- (5) C_1-C_{12} alkynyl, provided that a carbon of a
- carbon-carbon triple bond is not attached directly to L_3
- 25 when L_3 is other than a covalent bond,

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- (6) C₁-C₁₂ cycloalkyl,
- (7) heterocycle,
- (8) aryl

where (4)-(8) can be optionally substituted with 1, 2, 3, 4,
5 or 5 substituents independently selected from

(a) -OH, provided that no two -OH groups are
attached to the same carbon,

(b) -SH, provided that no two -SH groups are
attached to the same carbon,

10

(c) -CN,

(d) halo,

(e) -CHO,

(f) -NO₂,

(g) C₁-C₁₂ haloalkoxy,

15

(h) C₁-C₁₂ perfluoroalkoxy,

(i) -NR₁₃'R₁₄' where R₁₃' and R₁₄' are

selected from

(i) hydrogen,

(ii) C₁-C₁₂ alkanoyl,

20

(iii) C₁-C₁₂ alkoxycarbonyl,

(iv) C₁-C₁₂ alkoxycarbonyl substituted

with 1 to 2 phenyl substituents,

(v) C₁-C₁₂ cycloalkyl,

(vi) C₁-C₁₂ alkyl,

25

(vii) C₁-C₁₂ alkyl substituted with 1, 2,

or 3 substituents independently selected from C₁-C₁₂ alkoxy,

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C₃-C₁₂ cycloalkyl, and aryl,

(viii) C₃-C₁₂ alkenyl,

provided that a carbon of a carbon-carbon double bond is not directly attached to nitrogen,

5 (ix) C₃-C₁₂ alkynyl,

provided that a carbon of a carbon-carbon triple bond is not directly attached to nitrogen,

(x) aryl,

(xi) aryl substituted with 1, 2, 3, 4,

10 or 5 substituents independently selected from C₁-C₁₂ alkyl, C₁-C₁₂ alkanoyloxy, C₁-C₁₂ alkoxy, halo, -OH, provided that no two -OH groups are attached to the same carbon, thioalkoxy of one to twelve carbons, perfluoroalkyl of one to twelve carbons, -NR₁₂R₁₂', -CO₂R₁₅,
15 -OSO₂R₁₆, and (-X), or

R₁₃' and R₁₄' together with the nitrogen atom to which they are attached form a ring selected from

(i) aziridine,

(ii) azetidine,

20 (iii) pyrrolidine,

(iv) piperidine,

(v) pyrazine,

(vi) morpholine,

(vii) thiomorpholine, and

25 (viii) thiomorpholine sulfone

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where (i)-(viii) can be optionally substituted with 1, 2, or 3 C₁-C₁₂ alkyl,

(j) =NNR₁₃'R₁₄' ,

(k) -NR₁₂NR₁₃'R₁₄' ,

5

(l) -CO₂R₁₃ ,

(m) -C(X)NR₁₃'R₁₄' ,

(n) =N-OR₁₃ ,

(o) =NR₁₃ ,

(p) -S(O)_tR₁₅ ,

10

(q) -X'C(X)R₁₃ ,

(r) (-X) ,

(s) -O-(CH₂)_q-Z-R₁₅ where R₁₅ is as

previously defined, q is 1, 2, or 3, and Z is O or -S(O)_t- ,

(t) -OC(X)NR₁₃'R₁₄' ,

15

(u) -OSO₂R₁₆ ,

(v) C₁-C₁₂ alkanoyloxy ,

(w) -L_BR₃₀ where L_B is selected from

(i) a covalent bond ,

(ii) -O- ,

20

(iii) -S(O)_t- , and

(iv) -C(X)- and

R₃₀ is selected from

(i) C₁-C₁₂ alkyl ,

(ii) C₁-C₁₂ alkenyl ,

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provided that a carbon of a carbon-carbon double bond is not attached directly to L_3 when L_3 is other than a covalent bond,

(iii) C_1-C_{12} alkynyl, provided that a
5 carbon of a carbon-carbon triple bond is not attached directly to L_3 when L_3 is other than a covalent bond, where (i), (ii), and (iii) can be optionally substituted with C_3-C_{12} cycloalkyl, -OH, provided that no two -OH groups are attached to the same carbon, aryl, and heterocycle,

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(iv) aryl,

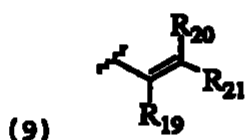
(v) aryl substituted with 1, 2, 3, 4,
or 5 substituents independently selected from C_1-C_{12} alkyl, halo, -NO₂, and -OH, provided that no two -OH groups are attached to the same carbon,

15

(vi) heterocycle, and

(vii) heterocycle substituted with 1, 2,
3, 4, or 5 substituents independently selected from
 C_1-C_{12} alkyl, halo, -NO₂, and -OH, provided that no two -OH groups are attached to the same carbon,

20

(x) $-X'C(X)X''R_{15}$,(y) $-C(=NR_7)OR_{15}$, and(z) $-NR_7(X)NR_{13}R_{14}$,

provided that when R_5 is (9), L_3 is other than

-NR₁₂- or -O-,

where the carbon-carbon double bond is in the Z or E configuration, and

R₁₉, R₂₀, and R₂₁ are independently selected from

- 5 (a) hydrogen,
- (b) halo,
- (c) C₁-C₁₂ alkyl, and
- (d) C₁-C₁₂ alkyl substituted with
- 10 (i) C₁-C₁₂ alkoxy,
- (ii) -OH, provided that no two -OH groups are attached to the same carbon,
- (iii) -SH, provided that no two -SH groups are attached to the same carbon,
- 15 (iv) -CN,
- (v) halo,
- (vi) -CHO,
- (vii) -NO₂,
- (viii) C₁-C₁₂ haloalkoxy,
- (ix) C₁-C₁₂ perfluoroalkoxy,
- 20 (x) -NR₁₃'R₁₄',
- (xi) =NNR₁₃'R₁₄',
- (xii) -NR₁₂NR₁₃'R₁₄',
- (xiii) -CO₂R₁₅,
- (xiv) -C(X)NR₁₃'R₁₄',
- 25 (xv) =N-OR₁₅,

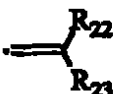
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(xvi) =NR₁₅,(xvii) -S(O)_tR₁₅,(xviii) -X'C(X)R₁₅,

(xix) (=X),

5 (xx) -O-(CH₂)_q-Z-R₁₅,(xxi) -OC(X)NR₁₃'R₁₄',(xxii) -LBR₃₀,(xxiii) C₁-C₁₂ alkanoyloxy,(xxiv) -OSO₂R₁₆, and10 (xxv) -NR₇(X)NR₁₃'R₁₄', orR₂₀ and R₂₁ together are selected from(a) C₃-C₁₂ cycloalkyl,(b) C₄-C₁₂ cycloalkenyl, and

(c)  (allene) where R₂₂ and R₂₃ are

independently hydrogen or C₁-C₁₂ alkyl, and

(10) C₄-C₁₂ cycloalkenyl carbons where the cycloalkenyl group or the ring formed by R₂₀ and R₂₁ together can be optionally substituted with one or two

20 substituents independently selected from

(a) C₁-C₁₂ alkoxy,

(b) -OH, provided that no two -OH groups are attached to the same carbon,

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(c) -SH, provided that no two -SH groups are attached to the same carbon,

(d) -CN,

(e) halo,

5

(f) -CHO,

(g) -NO₂,

(h) C1-C12 haloalkoxy,

(i) C1-C12 perfluoroalkoxy,

(j) -NR₁₃'R₁₄'

10

(k) -NMR₁₃'R₁₄',

(l) -NR₁₂NR₁₃'R₁₄',

(m) -CO₂R₁₅,

(n) -C(X)NR₁₃'R₁₄',

(o) =N-OR₁₅,

15

(p) =NR₁₅,

(q) -S(O)_tR₁₅,

(r) -X'C(X)R₁₅,

(s) (=X),

(t) -O-(CH₂)_q-Z-R₁₅,

20

(u) -OC(X)NR₁₃'R₁₄',

(v) -L_BR₃₀,

(w) C1-C12 alkanoyloxy,

(x) -OSO₂R₁₆, and

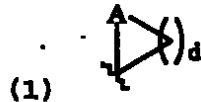
(y) -NR₇(X)NR₁₃'R₁₄';

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R₆ is hydrogen or C1-C12 alkyl; or

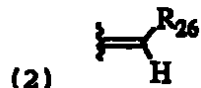
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-L₂-R₅ and R₆ together are



where d is 1, 2, 3, or 4 and A is selected from

- (a) -CH₂-,
- (b) -O-,
- (c) -S(O)_t, and
- (d) -NR₁₂-, or



where the carbon-carbon double bond can be in the E or Z configuration and R₂₆ is selected from

- (a) aryl,
- (b) heterocycle,
- (c) C1-C12 alkyl,
- (d) C3-C12 cycloalkyl,
- (e) C4-C12 cycloalkenyl, and
- (f) C4-C12 cycloalkenyl where (a)-(f) can be

optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from

- (i) C1-C12 alkoxy,
- (ii) -OH, provided that no two -OH
- (iii) -SH, provided that no two -SH
- (iv) -CN,

groups are attached to the same carbon,

groups are attached to the same carbon,

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- 5 (v) halo,
 (vi) -CHO,
 (vii) -NO₂,
 (viii) C₁-C₁₂ haloalkoxy,
 (ix) C₁-C₁₂ perfluoroalkoxy,
 (x) -NR₁₃'R₁₄',
 (xi) =NNR₁₃'R₁₄',
 (xii) -NR₁₂NR₁₃'R₁₄',
 (xiii) -CO₂R₁₅,
 10 (xiv) -C(X)NR₁₃'R₁₄',
 (xv) =N-OR₁₅,
 (xvi) =NR₁₅,
 (xvii) -S(O)_tR₁₅,
 (xviii) -X'C(X)R₁₅,
 15 (xix) (-X),
 (xx) -O-(CH₂)_q-Z-R₁₅',
 (xxi) -LgR₃₀,
 (xxii) C₁-C₁₂ alkanoyloxy,
 (xxiii) -OSO₂R₁₆, and
 20 (xxiv) -NR₁₂(X)NR₁₃'R₁₄';

R₁₀ and R₁₁ are independently selected from

- (i) hydrogen,
 (ii) C₁-C₁₂ alkanoyl;
 (iii) C₁-C₁₂ alkoxy carbonyl;

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(iv) C₁-C₁₂ alkoxy carbonyl and is substituted with 1 or 2 phenyl substituents,

(v) C₁-C₁₂ cycloalkyl,

(vi) C₁-C₁₂ alkyl,

5 (vii) C₁-C₁₂ alkyl substituted with 1, 2, or 3 substituents independently selected from C₁-C₁₂ alkoxy, C₃-C₁₂ cycloalkyl, and aryl,

(viii) C₃-C₁₂ alkenyl,

10 provided that a carbon of a carbon-carbon double bond is not directly attached to nitrogen,

(ix) C₃-C₁₂ alkynyl,

provided that a carbon of a carbon-carbon triple bond is not directly attached to nitrogen,

(x) aryl,

15 (xi) aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁-C₁₂ alkyl, C₁-C₁₂ alkanoyloxy, C₁-C₁₂ alkoxy carbonyl, C₁-C₁₂ alkoxy, halo, -OH, provided that no two -OH groups are attached to the same carbon, C₁-C₁₂ thioalkoxy, C₁-C₁₂ perfluoroalkyl, -NR₁₂R₁₂',

-CO₂R₁₅,

20 -OSO₂R₁₆, and

25 (-X),

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(xii) $-S(O)_t R_{35}$, where t is 0,1, or 2, and R_{35} is selected from(1) C_1-C_{12} alkyl,(2) C_2-C_{12} alkenyl,5 (3) C_2-C_{12} alkynyl where (1) - 3)

can be optionally substituted,

(4) $-OH$, and(5) $-NR_{12}R_{12'}$;10 R_{10} and R_{11} together with the nitrogen atom to which they are attached form a ring selected from

(i) aziridine,

(ii) azetidine,

(iii) pyrrolidine,

15 (iv) piperidine,

(v) pyrazine,

(vi) morpholine,

(vii) thiomorpholine, and

(viii) thiomorpholine sulfone

20 where (i) - (viii) can be optionally substituted with 1, 2, or 3 C_1-C_{12} alkyl, or25 R_{10} and R_7 together with the ring that they are attached form a 5-, 6-, or 7- membered ring with 0, 1, or 2 double bonds and 0-4 substituents selected from a group consisting of alkyl, halogen, or oxo; and

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R35 and R7 together with the ring that they are attached form a 5-, 6-, or 7- membered ring with 0, 1, or 2 double bonds and 0-4 substituents selected from a group consisting of C1-C12 alkyl, halogen, or oxo.

The present invention further relates to methods of selectively antagonizing or partially antagonizing the glucocorticoid receptor.

The present invention still further relates to methods of treating mammals with type II diabetes, and/or treating or one or more of the following symptoms of type II diabetes: hyperglycemia; hyperinsulinemia; inadequate glucose clearance; obesity; hypertension, or high glucocorticoid levels, by administering one or more compounds which antagonize the glucocorticoid receptor, preferably in the absence of compounds which agonize said receptor.

The present invention still further relates to methods of treating mammals with type II diabetes, and/or treating or one or more of the following symptoms of type II diabetes: hyperglycemia; hyperinsulinemia; inadequate glucose clearance; obesity; hypertension, or high glucocorticoid levels, by administering one or more compounds of formula I.

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The present invention additionally relates to
pharmaceutical compositions containing compounds of formula
I.

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Detailed Description of the Invention

The term "alkanoyl" refers to an alkyl group attached to the parent molecular group through a carbonyl group.

5 The term "alkanoyloxy" refers to an alkanoyl group attached to the parent molecular group through an oxygen atom.

10 The term "alkenyl" refers to a monovalent straight or branched chain group of two to twelve carbons derived from a hydrocarbon having at least one carbon-carbon double bond.

The term "alkoxy" refers to an alkyl group attached to the parent molecular group through an oxygen atom.

15 The term "alkoxycarbonyl" refers to an ester group, for example, an alkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "alkyl" refers to a monovalent straight or branched chain group of one to twelve carbons derived from a saturated hydrocarbon.

20 The term "alkylene" refers to a divalent straight or branched chain group of one to twelve carbons derived from an alkane.

The term "alkynyl" refers to a monovalent straight or branched chain hydrocarbon of two to twelve carbons with at least one carbon-carbon triple bond.

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The term "alkynylene" refers to a divalent straight or branched chain group of two to twelve carbons derived from an alkyne.

The term "amino" refers to -NH_2 .

5 The term "aryl" refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings. The aryl group can also be fused to a cyclohexane, cyclohexene, cyclopentane or cyclopentene ring.

The term "carboxy" refers to $\text{-CO}_2\text{H}$.

10 The term "cycloalkenyl" refers to a monovalent group derived from a cyclic or bicyclic hydrocarbon of three to twelve carbons that has at least one carbon-carbon double bond.

15 The term "cycloalkyl" refers to a monovalent group three to twelve carbons derived from a saturated cyclic or bicyclic hydrocarbon.

The term "halo" refers to F, Cl, Br, or I.

20 The term "heterocycle" represents a represents a 4-, 5-, 6-, or 7-membered ring containing one, two, or three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur. The 4- and 5-membered rings have zero to two double bonds, and the 6- and 7-membered rings have zero to three double bonds. The term "heterocycle" also includes bicyclic, tricyclic and
25 tetracyclic groups in which any of the above heterocyclic rings is fused to one or two rings independently selected

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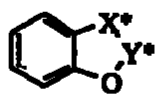
from an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring or another monocyclic heterocyclic ring. Heterocycles include acridinyl, benzimidazolyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, biotinyl, cinnolinyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, furyl, homopiperidinyl, imidazolidinyl, imidazolyl, imidazolyl, indolyl, isoquinolyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolidinyl, oxazolyl, piperazinyl, piperidinyl, pyranal, pyrazolidinyl, pyrazinyl, pyrazolyl, pyrazolinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinolinyl, quinoxaloyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydroquinolyl, tetrazolyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, thiomorpholinyl, triazolyl, and the like.

Heterocyclics also include bridged bicyclic groups wherein a monocyclic heterocyclic group is bridged by an alkylene group such as



Heterocyclics also include compounds of the formula

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where X* is selected from -CH₂-, -CH₂O- and -O-,
and Y* is selected from -C(O)- and -(C(Rⁿ)₂)_v -, where Rⁿ is
hydrogen or alkyl of one to four carbons, and v is 1-3.
These heterocycles include 1,3-benzodioxolyl, 1,4-
5 benzodioxanyl, and the like.

The term "heterocycloalkyl" as used herein, refers to a
non-aromatic, partially unsaturated or fully saturated 4- to
8-membered ring having from one or two heteroatoms
independently selected from oxygen, sulfur and nitrogen, in
10 which the nitrogen and sulfur heteroatoms can optionally be
oxidized and the nitrogen heteroatom can optionally be
quaternized.

The term "N-protected amino" refers to groups intended
to protect an amino group against undesirable reactions
15 during synthetic procedures. Commonly used N-protecting
groups are disclosed in Greene, "Protective Groups In
Organic Synthesis," (John Wiley & Sons, New York (1981)).
Preferred N-protecting groups are formyl, acetyl, benzoyl,
pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-
20 butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

The term "O-protected carboxy" refers to a carboxylic
acid protecting ester or amide group typically employed to
block or protect the carboxylic acid functionality while the
reactions involving other functional sites of the compound
25 are performed. Carboxy protecting groups are disclosed in

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Greene, "Protective Groups in Organic Synthesis" (1981).
Additionally, a carboxy protecting group can be used as a
prodrug whereby the carboxy protecting group can be readily
cleaved in vivo , for example by enzymatic hydrolysis, to
5 release the biologically active parent. Such carboxy
protecting groups are well known to those skilled in the
art, having been extensively used in the protection of
carboxyl groups in the penicillin and cephalosporin fields
as described in U.S. Pat. No. 3,840,556 and 3,719,667.

10 The term "oxo" refers to (=O).

The term "pharmaceutically acceptable prodrugs"
represents those prodrugs of the compounds of the present
invention which are, within the scope of sound medical
judgement, suitable for use in contact with the tissues of
15 humans and lower animals with undue toxicity, irritation,
allergic response, and the like, commensurate with a
reasonable benefit/risk ratio, and effective for their
intended use, as well as the zwitterionic forms, where
possible, of the compounds of the invention.

20 The term "prodrug" represents compounds which are
rapidly transformed in vivo to the parent compound of the
above formula, for example, by hydrolysis in blood. A
thorough discussion is provided in T. Higuchi and V. Stella,
Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S.
25 Symposium Series, and in Edward B. Roche, ed., Bioreversible
Carriers in Drug Design, American Pharmaceutical Association.

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and Pergamon Press, 1987, both of which are incorporated herein by reference.

The term "pharmaceutically acceptable salt" represents those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 66:1 - 19 (1977). The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphersulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pantoate, pectinate, persulfate, 3-phenylpropionate, phosphate, -----

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picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium,

5 potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like.

10 Compounds of the present invention can exist as stereoisomers where asymmetric or chiral centers are present. These compounds are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. The present invention
15 contemplates various stereoisomers and mixtures thereof. Stereoisomers include enantiomers and diastereomers, and equal mixtures of enantiomers are designated ($\pm$). Individual stereoisomers of compounds of the present invention can be prepared synthetically from commercially
20 available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral
25 auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and

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liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of enantiomers on chiral chromatographic columns.

Geometric isomers can also exist in the compounds of the present invention. The present invention contemplates the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a ring. Substituents around a carbon-carbon double bond are designated as being in the Z or E configuration where the term "Z" represents substituents on the same side of the carbon-carbon double bond and the term "E" represents substituents on opposite sides of the carbon-carbon double bond. The arrangement of substituents around a ring are designated as cis or trans where the term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds where the substituents are disposed on both the same and opposite sides of plane of the ring are designated cis/trans.

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Methods for Radioligand Binding Studies with Human
Glucocorticoid and Progesterone Receptor Cytosol

The procedure described in Anal. Biochem. 1970, 37,
5 244-252, hereby incorporated by reference, was used.
Briefly, cytosol preparations of human glucocorticoid
receptor- [GRX] isoform and human progesterone receptor-A
[PRA] isoform were obtained from Ligand Pharmaceuticals (San
Diego, CA). Both receptor cDNAs were cloned into
10 baculovirus expression vectors and expressed in insect SF21
cells. [³H]-dexamethasone (Dex, specific activity 82-86
Ci/mmol) and [³H]-progesterone (Prog, specific activity 97-
102 Ci/mmol) were purchased from Amersham Life Sciences
(Arlington Heights, IL). Glass fiber type C multiscreen
15 MAFC NOB plates were from Millipore (Burlington, MA).
Hydroxyapatite Bio-Gel HTP gel was from Bio-Rad Laboratories
(Hercules, CA). Tris(hydroxymethyl)aminomethane (Tris),
ethylenediaminetetraacetic acid (EDTA), glycerol,
dithiothreitol (DTT) and sodium molybdate were obtained
20 from Sigma Chemicals (St. Louis, MO). Microscint-20
scintillation fluid was from Packard Instrument (Meriden,
CT).

Stock solutions (32 mM) of compounds were prepared in
dimethylsulfoxide (DMSO), and 50X solutions of test
25 compounds were prepared from the 32 mM solution with a 50:50
mixture of DMSO/ethanol. The 50X solution was then diluted

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with binding buffer that contained 10 mM Tri-HCl, 1.5 mM EDTA, 10% glycerol, 1 mM DTT, 20 mM sodium molybdate, pH 7.5 @ 4°C. 1% DMSO/ethanol was present in the binding assay.

GRX and PRA binding reactions were performed in

5 Millipore Multiscreen plates. For GR binding assays, [³H]-Dex (~35,000 dpm (~0.9 nM)), GRX cytosol (~35 µg protein), test compounds and binding buffer were mixed in a total volume of 200 µL and incubated at 4 °C overnight in a plate shaker. Specific binding was defined as the difference
10 between binding of [³H]Dex in the absence and in the presence of 1µM unlabelled Dex.

For PR binding assays, [³H]Prog (~36,000 dpm (~0.8 nM)), PRA cytosol (~40 µg protein), test compounds and binding buffer were mixed in a total volume of 200 µL and
15 incubated at 4 °C at overnight in a plate shaker. Specific binding was defined as the difference between binding of [³H]Prog in the absence and in the presence of 3 µM unlabelled Prog.

After an overnight incubation, 50 µL of hydroxyapatite
20 (25 % weight/volume) slurry were added to each well and plates were incubated for 10 min at °C in a plate shaker. Plates were suctioned with a Millipore vacuum manifold and each well was rinsed with 300 µL of ice-cold binding buffer. A 250 µL aliquot of Packard Microscint-20 was added to each
25 well and the wells were shaken at room temperature for 20

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minutes. The amount of radioactivity was determined with a Packard TopCount plate reader.

Determination of Inhibition Constant (K_i)

5

The concentration of test compounds that inhibited 50% of specific binding (IC₅₀) was determined from a Hill analysis of the competitive binding experiments. The K_i of test compounds was determined using the Cheng-Prusoff equation $K_i = IC_{50} / (1 + [L^*] / [K_L])$ where L* is the concentration of radioligand and K_L is the dissociation constant of the radioligand determined from saturation analysis. For GRX, K_L was ~1.5 nM, and for PRA, K_L was ~4.5 nM. The inhibitory potencies of compounds of this invention and their selectivity for GR and PR receptors may be determined.

The present invention also provides pharmaceutical compositions, which comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions may be specially formulated for oral administration in solid or liquid form, for parenteral injection, or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally,

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intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray. The term "parenteral" administration refers to modes of administration which include intravenous, intramuscular, 5 intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, 10 suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable 15 mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of 20 the required particle size in the case of dispersions, and by the use of surfactants. Conversely, reduced particle size may maintain biological activity.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and 25 dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various

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antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the

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drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols,--

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sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers

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such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, 5 castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and 10 suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan 15 esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating 20 excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

25 Compounds of the present invention can also be administered in the form of liposomes. As is known in the

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art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers, or propellants which may be required. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic-response for a

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particular patient, compositions, and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

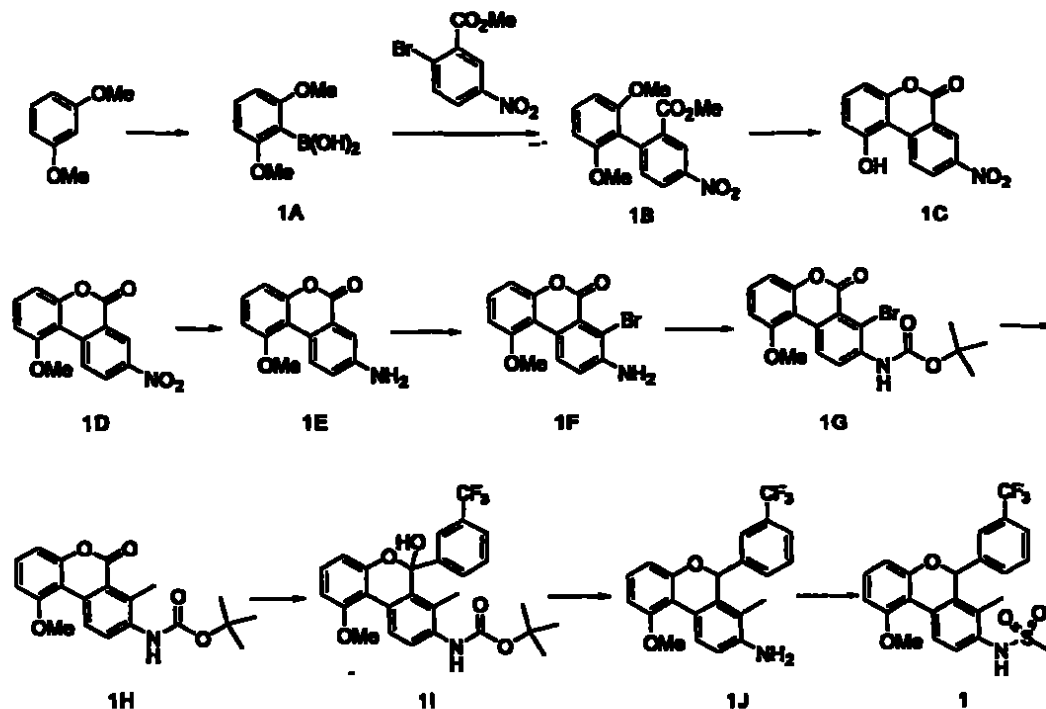
Generally dosage levels of about 1 to about 50, more preferably of about 5 to about 20 mg of active compound per kilogram of body weight per day are administered orally to a mammalian patient. If desired, the effective daily dose may be divided into multiple doses for purposes of administration, e.g. two to four separate doses per day.

Abbreviations that have been used in the descriptions of the scheme and the examples that follow are: $\text{BF}_3 \cdot \text{OEt}_2$ for boron trifluoride diethyl ether complex; DMF for N,N-dimethylformamide, DMSO for dimethylsulfoxide; and THF for tetrahydrofuran.

The compounds and processes of the present invention will be better understood in connection with the following synthetic Scheme which illustrates the methods by which the compounds of the invention can be prepared.

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Scheme I

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As exemplified in Scheme 1, resorcinol dimethyl ether can be metallated with a strong base such as *n*- or *sec*-butyllithium, treated with a trialkoxyborate such as trimethyl- or triisopropylborate and hydrolyzed with acid such as 2M HCl to provide boronic acid 1A. Treatment of 1A with methyl 5-nitro-2-bromobenzoate in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) or dichlorobis(triphenylphosphine)palladium (II) provides biphenyl 1B. Demethylation of 1B may be accomplished with

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reagents such as BBr_3 , to provide hydroxylactone 1C, which is then treated with alkylating agents such as methyl iodide to provide 1D. Conversion of 1D to amine 1E can be accomplished using hydrogen gas and a palladium catalyst

5 such as 10% palladium on carbon. Treatment of 1E with agents such as *N*-bromosuccinimide or pyridinium tribromide results in regioselective bromination to form 1F, which is protected as its *t*-butyl carbamate 1G by treatment with triphosgene and *t*-butyl alcohol. Conversion of 1G to 1H may

10 be accomplished using palladium catalysts such as [1,1-bis(diphenylphosphino)ferrocene-]dichloropalladium(II) or tetrakis(triphenylphosphine)palladium(0) in the presence of ligands such as tetramethyltin or isopropenyltrimethyltin. Introduction of functionalization at the C-5 position may be

15 achieved through addition of organometallic reagents such as 3-trifluoromethylphenylmagnesium bromide to the C-5 carbonyl of 1H to provide 1I, followed by deoxygenation with Lewis acids such as $\text{BF}_3 \cdot \text{OEt}_2$ and reducing agents such as triethylsilane to provide the free aniline 1J. Final

20 conversion of 1J to 1 may be accomplished by treatment of aniline 1J with methylsulfonyl chloride to provide sulfonamide 1.

Compounds of this invention include:

N-[1-methoxy-7-methyl-6-[3-(trifluoromethyl)phenyl]-6H-

25 dibenzo[b,d]pyran-6-yl]methanesulfonamide;

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N- (7-bromo-1-methoxy-6-phenyl-6H-dibenzo [b, d] pyran-6-yl) methanesulfonamide;

N- [7-bromo-1-methoxy-6- [3- (trifluoromethyl) phenyl] -6H-dibenzo [b, d] pyran-6-yl] methanesulfonamide;

- 5 N- [1-methoxy-7- (1-methylethenyl) -6- [3- (trifluoromethyl) phenyl] -6H-dibenzo [b, d] pyran-6-yl] methanesulfonamide; and
- N- [7-ethenyl-1-methoxy-6- [3- (trifluoromethyl) phenyl] -6H-dibenzo [b, d] pyran-6-yl] methanesulfonamide.

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166EXAMPLES

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Example 1A

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A solution of 1,3-dimethoxybenzene (33.2 g, 240 mmol) in hexanes (20 mL) at -20 °C was treated sequentially with n-butyllithium (100 mL of a 2.4 M solution in hexanes, 240 mmol) and N,N,N',N'-tetramethylethylenediamine (1.81 mL, 12 mmol), stirred at 23 °C for 1.5 hours, cooled to -78 °C, treated with triisopropylborate (60.9 mL, 264 mmol) in diethyl ether (60 mL) over 1.5 hours with additional diethyl ether (150 mL) added to maintain stirring, stirred at 23 °C for 2 hours, poured into ice (150 mL) and 3M HCl (150 mL), and extracted with ethyl acetate. The extract was dried (Na₂SO₄), filtered, and concentrated, during which a white solid precipitated from solution. The solid was collected by filtration and washed with hexanes to provide the desired compound.

MS (DCI/NH₃) m/z 200 (M+NH₄)⁺.

Example 1B

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A mixture of Example 1A, methyl 5-nitro-2-bromobenzoate (25.8 g, 99.2 mmol), (21.7 g, 119 mmol), cesium carbonate

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(97.1 g, 298 mmol), and dichlorobis-(triphenylphosphine)palladium(II) (3.5 g, 5.0 mmol) in DMF (300 mL) was stirred for 24 hours at 80 °C, cooled to 23 °C, treated with water (600 mL), and extracted with ethyl acetate (800 mL). The extract was dried (Na₂SO₄) and concentrated, during which a light yellow solid precipitated from solution. The mixture was placed in a freezer (-20 °C) for 2 hours then filtered to provide the desired compound. MS (DCI/NH₃) m/z 318 (M+H)⁺ and 335 (M+NH₄)⁺.

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Example 1C

A solution of Example 1B (11.1 g, 35.1 mmol) in dichloromethane (60 mL) at -78 °C was treated with boron tribromide (25.0 g, 99.8 mmol), warmed to 23 °C for 1 hour, recooled to -78 °C, and treated with methanol (100 mL). The mixture was warmed to 0 °C, and the precipitate was collected by filtration and recrystallized from methanol to provide the desired compound. MS (DCI/NH₃) m/z 275 (M+NH₄)⁺.

15
20Example 1D

A mixture of Example 1C (10.7 g, 41.6 mmol) and Cs₂CO₃ (20.0 g, 61.4 mmol) in DMF (130 mL) at 23 °C was treated

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dropwise with methyl iodide (22.8 g, 161 mmol), stirred for 4 hours, treated with water, and extracted with 1:1 ethyl acetate/hexane. The extract was concentrated, and the resulting solid was filtered, washed with water (100 mL), and dried under vacuum to provide the desired compound. MS (DCI/NH₃) m/z 289 (M+NH₄)⁺.

Example 1E

10 A suspension of Example 1D (11.2 g, 41.3 mmol) in dioxane (400 mL) at 23 °C was treated with 10% palladium on carbon (580 mg), heated at 65° C, treated with hydrogen, stirred under atmospheric pressure for 60 hours, filtered
15 through powdered sea shells (Celite®) while hot, and concentrated during which a precipitate formed. The product was filtered and dried under vacuum to provide the desired compound. Concentration of the mother liquor to half of its original volume afforded a second crop of desired compound.
20 MS (DCI/NH₃) m/z 242 (M+H)⁺ and 259 (M+NH₄)⁺.

Example 1F

25 A solution of Example 1E (3.0 g, 12.5 mmol) in dioxane (300 mL) and THF (100 mL) at 23 °C was treated with

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pyridinium tribromide (4.0 g, 12.5 mmol) portion-wise over 15 min, stirred at 23 °C for 14 h, treated with water (400 mL), and extracted with ethyl acetate (400 mL). The extract was dried (Na₂SO₄), treated with charcoal (2 g),

- 5 filtered through powdered sea shells (Celite®) and concentrated to provide the desired compound.

MS (DCI/NH₃) m/z 338 (M+NH₄)⁺.

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Example 1G

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A suspension of Example 1F (1.8 g, 5.7 mmol) and triphosgene (0.74 g, 2.5 mmol) in THF (300 mL) was heated at reflux for 3 h. The crude reaction mixture was concentrated to dryness, and volatile byproducts were removed on a high vacuum pump for 1 h. The residue was dissolved in THF (40mL) and t-butyl alcohol (250 mL), treated with triethylamine (0.58 g, 5.7 mmol), heated at 50 °C for 2 h, and concentrated. Flash chromatography of the residue on silica gel with 20% ethyl acetate/hexane provided the desired compound.

MS (DCI/NH₃) m/z 437 (M+NH₄)⁺.

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170Example 1H

A solution of Example 1G (1.0 g, 2.4 mmol) and (1,3-bis(diphenylphosphino)ferrocene)palladium (II) chloride·dichloromethane (220 mg, 0.27 mmol) in 1-methyl-2-pyrrolidinone (2 mL) was treated with isopropenyltrimethylstannane (0.98 g, 4.8 mmol), heated at 80 °C for 24 hours, cooled to room temperature, treated with saturated KF, and extracted with ethyl acetate. The extract was washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was purified by flash chromatography on silica gel with 5-15% ethyl acetate/hexanes to provide the desired compound.

MS (DCI/NH₃) m/z 373 (M+NH₄)⁺.

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Example 1I

A solution of Example 1H (0.29 g, 0.81 mmol) in THF (50 mL) at -30 °C was treated with a solution of 3-trifluoromethylphenylmagnesium bromide in diethyl ether (0.4 M, 12 mL, 4.9 mmol), warmed to 0 °C, stirred for 20 hours, treated with saturated NH₄Cl, warmed to 25 °C, and extracted with ethyl acetate. The extract was dried (Na₂SO₄), filtered, and concentrated. The residue was purified by

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flash chromatography on silica gel with 20% ethyl acetate/hexanes to provide the desired compound.

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Example 1J

A solution of Example 1I (0.1 g, 0.20 mmol) in dichloromethane (30 mL) at 0 °C was treated with triethylsilane (0.23 g, 2.0 mmol) and BF₃·OEt₂ (0.28 g, 2.0 mmol), warmed to room temperature, stirred for 16 hours, and treated with saturated NaHCO₃. The organic layer was dried (Na₂SO₄), filtered, and concentrated. The residue was purified by flash chromatography on silica gel with 20% ethyl acetate/hexanes to provide the desired compound.

15 MS (DCI/NH₃) m/z 386 (M+H)⁺;

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Example 1

20 A solution of 1J (0.025 g, 0.065 mmol) in dichloromethane (7 mL) at 0 °C was treated with methanesulfonyl chloride (0.006 mL, 0.075 mmol), warmed to room temperature, stirred for 14 hours, and treated with saturated NaHCO₃. The organic layer was dried (Na₂SO₄),

25 filtered, and concentrated. The residue was purified by

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flash chromatography on silica gel with 42% ethyl acetate/hexanes to provide the desired compound.

mp = 217 - 218 °C

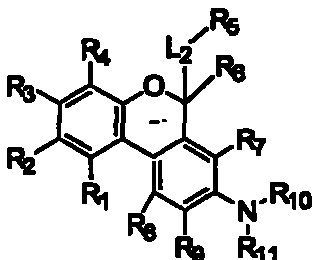
MS (DCI/NH₃) m/z 481 (M+NH₄)⁺, 464 (M+H)⁺;

5 ¹H NMR (300 MHz, DMSO-d₆) 9.25 (s, 1H), 8.3 (d, 1H), 7.61 (d, 1H), 7.55 (s, 1H), 7.50 (t, 1H), 7.41 (d, 1H), 7.28 (d, 1H), 7.12 (t, 1H), 6.7 (s, 1H), 6.69 (dd, 1H), 6.6 (dd, 1H), 3.85 (s, 3H), 3.02 (s, 3H), 2.2 (s, 3H);

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We Claim:

1. A compound of formula I



I,

or a pharmaceutically acceptable salt or prodrug thereof,

10 wherein:

R_1 is $L_1 - R_A$.

R₂, R₃, R₄, R₇, R₈, and R₉ are independently selected from -L₁-R_A or -H,

L₁ is selected from:

- (1) a covalent bond,
- (2) -O-,
- (3) -S(O)_t-, where t is 0, 1, or 2,
- (4) -C(X)-, where X is O or S,
- (5) -NR₁₂-, where R₁₂ is selected from
 - (a) hydrogen,
 - (b) aryl,
 - (c) C₁-C₁₂ cycloalkyl,
 - (d) C₁-C₁₂ alkanoyl,
 - (e) C₁-C₁₂ alkoxycarbonyl,

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(f) C_1-C_{12} alkoxycarbonyl substituted with 1 to 2 aryl groups,

(g) C_1-C_{12} alkyl,

(h) C_1-C_{12} alkyl substituted with 1 or 2 substituents independently selected from aryl or C_3-C_{12} cycloalkyl,

(i) C_3-C_{12} alkenyl, provided that a carbon of a carbon-carbon double bond is not attached directly to nitrogen,

10 (j) C_3-C_{12} alkynyl, provided that a carbon of a carbon-carbon triple bond is not attached directly to nitrogen,

(6) $-NR_{13}C(X)NR_{14}-$ where X is O or S and R_{13} and R_{14} are independently selected from

15 (a) hydrogen,

(b) aryl,

(c) C_3-C_{12} cycloalkyl,

(d) C_1-C_{12} alkyl,

(e) C_1-C_{12} alkyl substituted with 1 or 2

20 substituents independently selected from aryl or C_3-C_{12} cycloalkyl,

(f) C_3-C_{12} alkenyl,

provided that a carbon of a carbon-carbon double bond is not attached directly to nitrogen,

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(g) C_2-C_{11} alkynyl, provided that a carbon of a carbon-carbon triple bond is not attached directly to nitrogen,

(7) $-X'C(X)-$, wherein X is as previously defined
5 and X' is O or S,

(8) $-C(X)X'-$, wherein X and X' are as previously defined,

(9) $-X'C(X)X''-$, wherein X and X' are as previously defined, and X'' is O or S, provided that when X
10 is O, at least one of X' or X'' is O,

(10) $-NR_{13}C(X)-$,

(11) $-C(X)NR_{13}-$,

(12) $-NR_{13}C(X)X'-$,

(13) $-X'C(X)NR_{13}-$,

15 (14) $-SO_2NR_{13}-$,

(15) $-NR_{13}SO_2-$, and

(16) $-NR_{13}SO_2NR_{14}-$,

wherein (6)-(16) are drawn with their right ends attached to R_A ;

20 R_A is selected from

(1) $-OH$,

(2) $-OG$ where G is a $-OH$ protecting group,

(3) $-SH$,

(4) $-CN$,

25 (5) halo, ...

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- (6) haloalkoxy of one to twelve carbons,
- (7) perfluoroalkoxy of one to twelve carbons,
- (8) -CHO,
- (9) -NR₁₂R₁₂' where R₇ is defined previously and

5 R₁₂' is selected from

- (a) hydrogen,
- (b) aryl,
- (c) C₁-C₁₂ cycloalkyl,
- (d) C₁-C₁₂ alkanoyl,
- (e) C₁-C₁₂ alkoxy carbonyl,
- (f) C₁-C₁₂ alkoxy carbonyl substituted with 1

or 2 aryl groups,

- (g) C₁-C₁₂ alkyl,
- (h) C₁-C₁₂ alkyl substituted with 1 or 2

15 substituents independently selected from aryl or C₁-C₁₂ cycloalkyl,

(i) C₁-C₁₂ alkenyl, provided that a carbon of a carbon-carbon double bond is not attached directly to nitrogen,

20 (j) C₁-C₁₂ alkynyl, provided that a carbon of a carbon-carbon triple bond is not attached directly to nitrogen,

(10) -C(X)NR₁₃R₁₄,

(11) -OSO₂R₁₅ where R₁₅ is selected from

- 25
- (a) aryl,
 - (b) C₁-C₁₂ cycloalkyl,

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(c) C_1-C_{12} alkyl,(d) C_1-C_{12} alkyl substituted with 1, 2, 3, or 4 halo substituents, and(e) C_1-C_{12} perfluoroalkyl, provided that when
5 R_A is (1) to (11), L_1 is a covalent bond,(12) C_1-C_{12} alkyl, ..(13) C_2-C_{12} alkenyl, provided that a carbon of a carbon-carbon double bond is not attached directly to L_1 when L_1 is other than a covalent bond,10 (14) C_1-C_{12} alkynyl, provided that a carbon of a carbon-carbon triple bond is not attached directly to L_1 when L_1 is other than a covalent bond, where (12), (13), and (14) can be optionally substituted with 1, 2, or 3 substituents independently selected from15 (a) C_1-C_{12} alkoxy,

(b) -OH, provided that no two -OH groups are attached to the same carbon,

(c) -SH, provided that no two -SH groups are attached to the same carbon,

20 (d) -CN,

(e) halo,

(f) -CHO,

(g) -NO₂,(h) C_1-C_{12} haloalkoxy,25 (i) C_1-C_{12} perfluoroalkoxy,09388251-090199
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(j) $-\text{NR}_{12}\text{R}_{12}'$,

(k) $-\text{NNR}_{12}\text{R}_{12}'$,

(l) $-\text{NR}_{12}\text{NR}_{12}'\text{R}_{12}''$ where R_{12} and R_{12}' are as previously defined and R_{12}'' is selected from

5 (i) hydrogen,

(ii) aryl,

(iii) $\text{C}_1\text{-C}_{12}$ cycloalkyl,

(iv) $\text{C}_1\text{-C}_{12}$ alkanoyl,

(v) $\text{C}_1\text{-C}_{12}$ alkoxy carbonyl,

10 (vi) $\text{C}_1\text{-C}_{12}$ alkoxy carbonyl substituted with 1 or 2 aryl groups,

(vii) $\text{C}_1\text{-C}_{12}$ alkyl,

(viii) $\text{C}_1\text{-C}_{12}$ alkyl substituted with 1 or 2 substituents independently selected from aryl or $\text{C}_1\text{-C}_{12}$

15 cycloalkyl,

(ix) $\text{C}_1\text{-C}_{12}$ alkenyl, provided that a carbon-carbon double bond is not attached directly to nitrogen, and

(x) $\text{C}_1\text{-C}_{12}$ alkynyl, provided that a
20 carbon-carbon triple bond is not attached directly to nitrogen,

(m) $-\text{CO}_2\text{R}_{16}$ where R_{16} is selected from

(i) aryl,

(ii) aryl substituted with 1, 2, or 3

25 $\text{C}_1\text{-C}_{12}$ alkyl,

(ii) $\text{C}_1\text{-C}_{12}$ cycloalkyl,

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(iii) C_1-C_{12} alkyl, and(iv) C_1-C_{12} alkyl substituted with aryl or C_3-C_{12} cycloalkyl,(n) $-C(X)NR_{13}R_{14}$,5 (o) $=N-OR_{16}$,(p) $=NR_{16}$,(q) $-S(O)_tR_{16}$,(r) $-X'C(X)R_{16}$,(s) $(=X)$, and10 (t) $-OSO_2R_{16}$,(15) C_3-C_{12} cycloalkyl,(16) C_4-C_{12} cycloalkenyl,

provided that a carbon of a carbon-carbon double bond is not attached directly to L_1 when L_1 is other than a covalent bond,

15 where (15) and (16) can be optionally substituted with 1, 2, 3, or 4 substituents independently selected from

(a) C_1-C_{12} alkyl,

(b) aryl,

20 (c) C_1-C_{12} alkoxy,

(d) halo, and

(e) $-OH$, provided that no two $-OH$ groups are attached to the same carbon,

(17) C_1-C_{12} perfluoroalkyl,

25 (18) aryl, and — — — — —

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(19) heterocycle

where (18) and (19) can be optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from

- 5 (a) C_1-C_{12} alkyl,
 (b) C_1-C_{12} alkanoyloxy,
 (c) C_1-C_{12} alkoxycarbonyl,
 (d) C_1-C_{12} alkoxy,
 (e) halo,
 (f) -OH,

10 provided that no two -OH groups are attached to the same carbon,

- (g) C_1-C_{12} thioalkoxy,
 (h) C_1-C_{12} perfluoroalkyl,
 (i) $-NR_{12}R_{12}'$,
 15 (j) $-CO_2R_{16}$,
 (k) $-OSO_2R_{16}$, and
 (l) $(=X)$; or

20 R_1 and R_2 together are $-X^*-Y^*-Z^*-$ where X^* is -O- or $-CH_2-$, Y^* is $-C(O)-$ or $-(C(R_{17})(R_{18}))_v-$ where R_{17} and R_{18} are independently hydrogen or C_1-C_{12} alkyl and v is 1, 2, or 3, and Z^* is selected from $-CH_2-$, $-CH_2S(O)t-$, $-CH_2O-$, $-CH_2NR_{12}-$, $-NR_{12}-$, and -O-;

25 L_2 is selected from

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- (1) a covalent bond,
- (2) C_1-C_{12} alkylene,
- (3) C_1-C_{12} alkylene substituted with 1 or 2 substituents independently selected from

- 5 (a) C_1-C_2 spiroalkyl,
- (b) C_1-C_2 spiroalkenyl,
- (c) oxo,
- (d) halo, and
- (e) -OH, provided that no two -OH groups are
- 10 attached to the same carbon,

- (4) C_1-C_{12} alkynylene,
- (5) -NR₁₂-,
- (6) -C(X)-,
- (7) -O-, and
- 15 (8) -S(O)_t-; and

R₅ is selected from

- (1) halo,
- (2) -C(=NR₁₂)OR₁₅,
- 20 (3) -CN, provided that when R₅ is (1), (2), or
- (3), L₂ is a covalent bond,
- (4) C_1-C_{12} alkyl,
- (5) C_1-C_{12} alkynyl, provided that a carbon of a
- carbon-carbon triple bond is not attached directly to L₃
- 25 when L₃ is other than a covalent bond, -----

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- (6) C₁-C₁₂ cycloalkyl,
- (7) heterocycle,
- (8) aryl

where (4)-(8) can be optionally substituted with 1, 2, 3, 4,
5 or 5 substituents independently selected from

(a) -OH, provided that no two -OH groups are
attached to the same carbon,

(b) -SH, provided that no two -SH groups are
attached to the same carbon,

10

(c) -CN,

(d) halo,

(e) -CHO,

(f) -NO₂,

(g) C₁-C₁₂ haloalkoxy,

15

(h) C₁-C₁₂ perfluoroalkoxy,

(i) -NR₁₃'R₁₄' where R₁₃' and R₁₄' are

selected from

(i) hydrogen,

(ii) C₁-C₁₂ alkanoyl,

20

(iii) C₁-C₁₂ alkoxy carbonyl,

(iv) C₁-C₁₂ alkoxy carbonyl substituted

with 1 to 2 phenyl substituents,

(v) C₁-C₁₂ cycloalkyl,

(vi) C₁-C₁₂ alkyl,

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(vii) C₁-C₁₂ alkyl substituted with 1, 2,

or 3 substituents independently selected from C₁-C₁₂ alkoxy,

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C₁-C₁₂ cycloalkyl, and aryl,

(viii) C₁-C₁₂ alkenyl,

provided that a carbon of a carbon-carbon double bond is not directly attached to nitrogen,

5 (ix) C₁-C₁₂ alkynyl,

provided that a carbon of a carbon-carbon triple bond is not directly attached to nitrogen,

(x) aryl,

(xi) aryl substituted with 1, 2, 3, 4,

10 or 5 substituents independently selected from C₁-C₁₂ alkyl, C₁-C₁₀ alkanoyloxy, C₁-C₁₂ alkoxy, halo, -OH, provided that no two -OH groups are attached to the same carbon, thioalkoxy of one to twelve carbons, perfluoroalkyl of one to twelve carbons, -NR₁₂R₁₂', -CO₂R₁₅,
15 -OSO₂R₁₆, and (-X), or R₁₃' and R₁₄' together with the nitrogen atom to which they are attached form a ring selected from

(i) aziridine,

(ii) azetidine,

20 (iii) pyrrolidine,

(iv) piperidine,

(v) pyrazine,

(vi) morpholine,

(vii) thiomorpholine, and

25 (viii) thiomorpholine sulfone

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where (i)-(viii) can be optionally substituted with 1, 2, or 3 C₁-C₁₂ alkyl,

- (j) -NNR₁₃'R₁₄',
- (k) -NR₁₂NR₁₃'R₁₄',
- 5 (l) -CO₂R₁₃,
- (m) -C(X)NR₁₃'R₁₄',
- (n) -N-OR₁₃,
- (o) -NR₁₃,
- (p) -S(O)_tR₁₅,
- 10 (q) -X'C(X)R₁₃,
- (r) (-X),
- (s) -O-(CH₂)_q-Z-R₁₅ where R₁₅ is as previously defined, q is 1, 2, or 3, and Z is O or -S(O)_t-,
- (t) -OC(X)NR₁₃'R₁₄',
- 15 (u) -OSO₂R₁₆,
- (v) C1-C12 alkanoyloxy,
- (w) -L_BR₃₀ where L_B is selected from
- (i) a covalent bond,
- (ii) -O-,
- 20 (iii) -S(O)_t-, and
- (iv) -C(X)- and

R₃₀ is selected from

- (i) C1-C12 alkyl,
- (ii) C1-C12 alkenyl,

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provided that a carbon of a carbon-carbon double bond is not attached directly to L_3 when L_3 is other than a covalent bond,

(iii) C_1-C_{12} alkynyl, provided that a carbon of a carbon-carbon triple bond is not attached directly to L_3 when L_3 is other than a covalent bond, where (i), (ii), and (iii) can be optionally substituted with C_1-C_{12} cycloalkyl, -OH, provided that no two -OH groups are attached to the same carbon, aryl, and heterocycle,

(iv) aryl,

(v) aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_1-C_{12} alkyl, halo, -NO₂, and -OH, provided that no two -OH groups are attached to the same carbon,

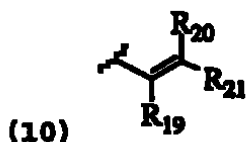
(vi) heterocycle, and

(vii) heterocycle substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_1-C_{12} alkyl, halo, -NO₂, and -OH, provided that no two -OH groups are attached to the same carbon,

(x) $-X'C(X)X'R_{15}$,

(y) $-C(=NR_7)OR_{15}$, and

(z) $-NR_7(X)NR_{13}'R_{14}'$,



provided that when R_5 is (9), L_3 is other than

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-NR₁₂- or -O-,

where the carbon-carbon double bond is in the Z or E configuration, and

R₁₉, R₂₀, and R₂₁ are independently selected from

- 5 (a) hydrogen,
- (b) halo, --
- (c) C₁-C₁₂ alkyl, and
- (d) C₁-C₁₂ alkyl substituted with
- 10 (i) C₁-C₁₂ alkoxy,
- (ii) -OH, provided that no two -OH groups are attached to the same carbon,
- (iii) -SH, provided that no two -SH groups are attached to the same carbon,
- 15 (iv) -CN,
- (v) halo,
- (vi) -CHO,
- (vii) -NO₂,
- (viii) C₁-C₁₂ haloalkoxy,
- (ix) C₁-C₁₂ perfluoroalkoxy,
- 20 (x) -NR₁₃'R₁₄'
- (xi) =NNR₁₃'R₁₄',
- (xii) -NR₁₂NR₁₃'R₁₄',
- (xiii) -CO₂R₁₅,
- (xiv) -C(X)NR₁₃'R₁₄',
- 25 (xv) =N-OR₁₅, ...

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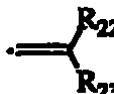
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(xvi) -NR_{15} ,(xvii) $\text{-S(O)}_t\text{R}_{15}$,(xviii) $\text{-X}'\text{C(X)}\text{R}_{15}$,(xix) $(=\text{X})$,

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(xx) $\text{-O-(CH}_2)_q\text{-Z-R}_{15}$,(xxi) $\text{-OC(X)NR}_{13}\text{'R}_{14}'$,(xxii) $\text{-L}_3\text{R}_{30}$,(xxiii) $\text{C}_1\text{-C}_{12}$ alkanoyloxy,(xxiv) $\text{-OSO}_2\text{R}_{16}$, and

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(xxv) $\text{-NR}_7(\text{X})\text{NR}_{13}\text{'R}_{14}'$, or R_{20} and R_{21} together are selected from(a) $\text{C}_1\text{-C}_{12}$ cycloalkyl,(b) $\text{C}_4\text{-C}_{12}$ cycloalkenyl, and(c)  (allene) where R_{22} and R_{23} are

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independently hydrogen or $\text{C}_1\text{-C}_{12}$ alkyl, and(10) $\text{C}_4\text{-C}_{12}$ cycloalkenyl carbons where the cycloalkenyl group or the ring formed by R_{20} and R_{21}

together can be optionally substituted with one or two

20

substituents independently selected from

(a) $\text{C}_1\text{-C}_{12}$ alkoxy,(b) -OH , provided that no two -OH groups are attached to the same carbon,

(c) -SH, provided that no two -SH groups are attached to the same carbon,

- (d) -CN,
- (e) halo,
- (f) -CHO,
- (g) -NO₂,
- (h) C1-C12 haloalkoxy,
- (i) C1-C12 perfluoroalkoxy,
- (j) -NR₁₃'R₁₄'
- (k) =NNR₁₃'R₁₄' ,
- (l) -NR₁₂NR₁₃'R₁₄' ,
- (m) -CO₂R₁₅,
- (n) -C(X)NR₁₃'R₁₄' ,
- (o) =N-OR₁₅,
- (p) =NR₁₅,
- (q) -S(O)_tR₁₅,
- (r) -X'C(X)R₁₅,
- (s) (-X) ,
- (t) -O-(CH₂)_q-Z-R₁₅,
- (u) -OC(X)NR₁₃'R₁₄' ,
- (v) -LgR₃₀,
- (w) C1-C12 alkanoyloxy,
- (x) -OSO₂R₁₆, and
- (y) -NR₇(X)NR₁₃'R₁₄' ;

R₆ is hydrogen or C1-C12 alkyl; or

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-L₂-R₅ and R₆ together are



where d is 1, 2, 3, or 4 and A is selected from

- (a) -CH₂-,
- (b) -O-,
- (c) -S(O)_t, and
- (d) -NR₁₂-, or



where the carbon-carbon double bond can be in the E or Z configuration and R₂₆ is selected from

- (a) aryl,
- (b) heterocycle,
- (c) C₁-C₁₂ alkyl,
- (d) C₃-C₁₂ cycloalkyl,
- (e) C₄-C₁₂ cycloalkenyl, and
- (f) C₄-C₁₂ cycloalkenyl where (a)-(f) can be

optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from

- (i) C₁-C₁₂ alkoxy,
- (ii) -OH, provided that no two -OH
- (iii) -SH, provided that no two -SH
- (iv) -CN,

groups are attached to the same carbon,

groups are attached to the same carbon,

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- (v) halo,
- (vi) -CHO,
- (vii) -NO₂,
- (viii) C₁-C₁₂ haloalkoxy,
- (ix) C₁-C₁₂ perfluoroalkoxy,
- (x) -NR₁₃'R₁₄'
- (xi) -NNR₁₃'R₁₄'
- (xii) -NR₁₂NR₁₃'R₁₄'
- (xiii) -CO₂R₁₅,
- (xiv) -C(X)NR₁₃'R₁₄'
- (xv) -N-OR₁₅,
- (xvi) -NR₁₅,
- (xvii) -S(O)_tR₁₅,
- (xviii) -X'C(X)R₁₅,
- (xix) (-X),
- (xx) -O-(CH₂)_q-Z-R₁₅'
- (xxi) -L_BR₃₀,
- (xxii) C₁-C₁₂ alkanoyloxy,
- (xxiii) -OSO₂R₁₆, and
- (xxiv) -NR₁₂(X)NR₁₃'R₁₄'

R₁₀ and R₁₁ are independently selected from

- (i) hydrogen,
- (ii) C₁-C₁₂ alkanoyl;
- (iii) C₁-C₁₂ alkoxycarbonyl;

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(iv) C₁-C₁₂ alkoxy carbonyl and is substituted with 1 or 2 phenyl substituents,

(vi) C₁-C₁₂ cycloalkyl,

(vi) C₁-C₁₂ alkyl,

5 (vii) C₁-C₁₂ alkyl substituted with 1, 2, or 3 substituents independently selected from C₁-C₁₂ alkoxy, C₃-C₁₂ cycloalkyl, and aryl,

(viii) C₃-C₁₂ alkenyl,

10 provided that a carbon of a carbon-carbon double bond is not directly attached to nitrogen,

(ix) C₃-C₁₂ alkynyl,

provided that a carbon of a carbon-carbon triple bond is not directly attached to nitrogen,

(x) aryl,

15 (xi) aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁-C₁₂ alkyl, C₁-C₁₂ alkanoyloxy, C₁-C₁₂ alkoxy carbonyl, C₁-C₁₂ alkoxy, halo, -OH, provided that no two -OH groups are attached to the same carbon, C₁-C₁₂ thioalkoxy, C₁-C₁₂ perfluoroalkyl, -NR₁₂R₁₂',

-CO₂R₁₅,

-OSO₂R₁₆, and

25 (-X),

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(xii) $-S(O)_tR_{35}$, where t is 0,1, or 2, and R_{35} is selected from(1) C_1-C_{12} alkyl,(2) C_1-C_{12} alkenyl,5 (3) C_1-C_{12} alkynyl where (1) - 3)

can be optionally substituted,

(4) $-OH$, and(5) $-NR_{12}R_{12'}$;10 R_{10} and R_{11} together with the nitrogen atom to which
they are attached form a ring selected from

(i) aziridine,

(ii) azetidine,

(iii) pyrrolidine,

15 (iv) piperidine,

(v) pyrazine,

(vi) morpholine,

(vii) thiomorpholine, and

(viii) thiomorpholine sulfone

20 where (i)-(viii) can be optionally substituted with 1, 2, or
3 C_1-C_{12} alkyl, or25 R_{10} and R_7 together with the ring that they are
attached form a 5-, 6-, or 7- membered ring with 0, 1, or 2
double bonds and 0-4 substituents selected from a group
consisting of alkyl, halogen, or oxo; and09388251.090199
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R₃₅ and R₇ together with the ring that they are attached form a 5-, 6-, or 7- membered ring with 0, 1, or 2 double bonds and 0-4 substituents selected from a group consisting of C₁-C₁₂ alkyl, halogen, or oxo.

2. A compound according to Claim 1 where

R₁ is -L₁-R_A where

L₁ is selected from

- (1) a covalent bond,
 - (2) -O-,
 - (3) -C(X)X'- where X and X' are O,
 - (4) -X'C(X)- where X and X' are O, and
 - (5) -X'C(X)X"- where X, X', and X" are O and
- R_A is selected from
- (1) alkyl of one to twelve carbons,
 - (2) alkenyl of two to twelve carbons,
 - (3) alkynyl of two to twelve carbons where (1)-(3) can be optionally substituted,
 - (4) -OH, and
 - (5) -NR₁₂R₁₂';

R₂ is hydrogen or -L₁-R_A where L₁ is -O- and R_A is alkyl of one to twelve carbons;

R₃, R₄, R₈, and R₉ are hydrogen,

L₂ is a covalent bond or -NR₁₂-;

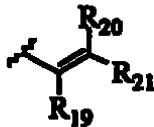
R₅ is selected from

- (1) halo,
- (2) -C(=NR₇)OR₁₀;
- (3) -CN,

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- (4) alkyl of one to twelve carbons,
- (5) alkynyl of two to twelve carbons,
- (6) heterocycle,
- (7) aryl,



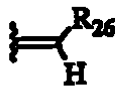
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- (8) , and

(9) cycloalkenyl of four to twelve carbons
where (4)-(7), (9), and the substituents defined by
R₁₉, R₂₀, and R₂₁ in (8) can be
optionally substituted; and

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R₅ is hydrogen; or



-L₂-R₅ and R₆ together are where the
substituents defined by R₂₆ can be optionally
substituted.

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R₇ is hydrogen; or R₇ and R₁₀ together with the ring
that they are attached form a 5-, 6-, or 7-membered
ring with 1-2 double bonds and 0-4 substituents selected from
a group consisting of alkyl, halogen, or oxo.

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R₁₀ and R₁₁ are independantly selected from hydrogen; -
C(O)R₃₃, or -S(O)_tR₃₅, where t is 0, 1, or 2, and R₃₅ is
selected from

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- (1) alkyl of one to twelve carbons,
- (2) alkenyl of two to twelve carbons,
- (3) alkynyl of two to twelve carbons where (1)-
(3) can be optionally substituted,
- (4) -OR₃₃, and
- (5) -NR₁₂R_{12'}; or

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3. A compound according to Claim 2 where L_1 is O and R_A is alkyl of one to twelve carbons that can be optionally substituted.

4. A compound according to Claim 3 where R_{10} is selected from $S(O)_t R_{35}$, where t is 0, 1, or 2, and R_{35} is selected from alkyl of one to four carbons.

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5. A compound according to Claim 4 selected from
N-[1-methoxy-7-methyl-6-[3-(trifluoromethyl)phenyl]-6H-dibenzo[b,d]pyran-6-yl]methanesulfonamide;

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N-(7-bromo-1-methoxy-6-phenyl-6H-dibenzo[b,d]pyran-6-yl)methanesulfonamide;

N-[7-bromo-1-methoxy-6-[3-(trifluoromethyl)phenyl]-6H-dibenzo[b,d]pyran-6-yl]methanesulfonamide;

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N-[1-methoxy-7-(1-methylethenyl)-6-[3-(trifluoromethyl)phenyl]-6H-dibenzo[b,d]pyran-6-yl]methanesulfonamide;

N-[7-ethenyl-1-methoxy-6-[3-(trifluoromethyl)phenyl]-6H-dibenzo[b,d]pyran-6-yl]methanesulfonamide; and

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N-[7-bromo-1-methoxy-6-(3,5-dimethylphenyl)-6H-dibenzo[b,d]pyran-6-yl]methanesulfonamide.

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6. A method of selectively modulating the antagonism effects of the glucocorticoid receptor in a mammal comprising administering an effective amount of a compound of Claim 1.

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7. A method of treating diabetes in a mammal comprising administering an effective amount of a compound of Claim 1.

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8. A method of treating diabetes in a mammal comprising administering an effective amount of a glucocorticoid receptor antagonist.

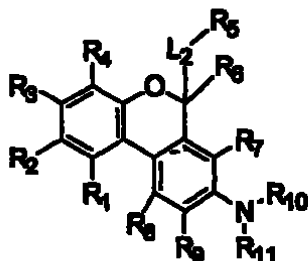
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9. A method according to Claim 8, wherein said glucocorticoid receptor antagonist is administered in the absence of a glucocorticoid receptor agonist.

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Abstract

The instant invention relates to compounds of formula I



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I

- 10 which are useful as antagonists of the glucocorticoid receptor and for treating diabetes in a mammal. In addition, any glucocorticoid receptor antagonist(s) is useful for the treatment of diabetes.

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Philip Kym, et al.

Express Mail No. KE835508206US

Serial No.:

I hereby certify that this paper
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Title: GLUCOCORTICOID RECEPTOR
ANTAGONISTS FOR TREATMENT OF
DIABETES

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231, on:

Case No.: 6577.US.01

Group Art No.: (not yet assigned)

Date of Deposit: September 1, 1999

Examiner: (not yet assigned)

Janille D. Strode

Date

Declaration and Power of Attorney
for a United States Patent Application

As a below-named inventor, I hereby declare that I believe I
am the original, first and joint inventor of the subject
matter which is claimed and for which a patent is sought on
the invention entitled GLUCOCORTICOID RECEPTOR ANTAGONISTS FOR
TREATMENT OF DIABETES, the specification of which is enclosed
herewith.

My residence, post office address and citizenship are as
stated below next to my name.

I hereby state that I have reviewed and understand the
contents of the above-mentioned specification, including the
claims.

I acknowledge a duty to disclose to the Patent and Trademark
Office all information known to me to be material to
patentability as defined in Title 37, Code of Federal
Regulations, §1.56.

Claim to benefit of foreign application(s) as follows:

I hereby claim foreign priority benefits under 35 U.S.C. §119
for the following foreign applications for patent or

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Page 1

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for the following foreign applications for patent or inventor's certificate.

NONE

The following foreign applications for patent or inventor's certificate have a filing date earlier than the filing date of the applications identified above.

NONE

Claim to benefit of earlier U.S. application(s) as follows:

I hereby claim the benefit under 35 U.S.C. §120 of the following earlier-filed United States patent applications. Insofar as the subject matter of each of the claims of this application is not disclosed in the prior U.S. applications in the manner required by 35 U.S.C. §112, first paragraph, I acknowledge a duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. §1.56 which came into existence between the filing date(s) of the prior applications and the national or PCT filing date of this application.

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

NONE

I hereby appoint the following Attorneys and/or agents to prosecute this application and any continuation or divisional applications based hereon, and to transact all business in the Patent and Trademark Office connected therewith:

09388251-090199

Mona Anand, Reg. No. 34,537
 Regina M. Anderson, Reg. No. 35,820
 Mark C. Bach, Reg. No. 34,766
 Cheryl L. Becker, Reg. No. 35,441
 Thomas D. Brainard, Reg. No. 32,459
 Dianne Casuto, Reg. No. 40,943
 Portia Chen, Reg. No. P44,075
 Steven R. Crowley, Reg. No. 31,604
 Andreas M. Danckers, Reg. No. 32,652
 J. Michael Dixon, Reg. No. 32,410
 Mimi C. Goller, Reg. No. 39,046
 Daniel J. Hulseberg, Reg. No. 36,554
 Neal D. Marcus, Reg. No. 35,267
 James D. McNeil, Reg. No. 26,204
 Robert A. Miller, Reg. No. 26,956
 Lawrence S. Pope, Reg. No. 26,791
 Nicholas A. Poulos, Reg. No. 30,209
 Dugal S. Sickert, Reg. No. 33,784
 Gregory W. Steele, Reg. No. 33,796
 Janelle D. Strode, Reg. No. 34,738
 Michael J. Ward, Reg. No. 37,960
 David L. Weinstein, Reg. No. 28,128
 Steven F. Weinstock, Reg. No. 30,117
 Brian R. Woodworth, Reg. No. 33,137
 Paul D. Yasger, Reg. No. 37,477

Send correspondence to: Steven F. Weinstock
 Abbott Laboratories
 D-377/AP6D
 100 Abbott Park Road
 Abbott Park, Illinois 60064-3500

Direct telephone calls to: Janelle D. Strode
 (847) 937-4395

INVENTORS

Name: (first, middle, last): Philip R. Kym
 Post Office Address: 141 Hillside Avenue
 Grayslake, IL 60030
 Residence: 141 Hillside Avenue
 Grayslake, IL 60030
 Citizenship: United States of America

Name: (first, middle, last): Benjamin C. Lane
 Post Office Address: 1284 Deer Trial Lane
 Libertyville, IL 60048
 Residence: 1284 Deer Trial Lane
 Libertyville, IL 60048
 Citizenship: United States of America

Name: (first, middle, last): John K. Pratt
 Post Office Address: 8210 61st Avenue
 Kenosha, WI 53142
 Residence: 8210 61st Avenue
 Kenosha, WI 53142
 Citizenship: United States of America

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Name: (first, middle, last): Tom von Geldern
Post Office Address: 4209 West Solon Road
Richmond, IL 60071
Residence: 4209 West Solon Road
Richmond, IL 60071
Citizenship: United States of America

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that all statements made herein were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Philip R. Kym 9/1/1999
Philip R. Kym Date

John K. Pratt 9-1-1999
John K. Pratt Date

Benjamin C. Lane 9/1/1999
Benjamin C. Lane Date

Tom von Geldern Date

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Octubre 05, 2000
Traducción Oficial No.0302
REF: ABBOTT LABORATORIES

Expediente No. 00.065.017

Certificación No. 2444, expedida por el Consulado de Colombia en
Washington, D.C., Estados Unidos, en la fecha de Septiembre 16 del año
2000, con firma del Cónsul de Colombia, Dra. Consuelo Sanchez Duran.
Hay sello del Consulado de Colombia en la ciudad de Washington, Estados
Unidos de América.

Sellos de Legalización: Ministerio de Relaciones Exteriores, No.447123, Firma
el Cónsul de Colombia, Consuelo Sanchez Durán

Sellos de Legalización: Ministerio de Relaciones Exteriores, fecha Octubre 4,
del año 2000, Hora: 12:29, Firma Jefe de Legalizaciones de Santafé de
Bogotá, D. C. Firma ilegible.

Eduardo Calado Viqueza
Eduardo Calado Viqueza
Jefe de Legalizaciones
Ministerio de Relaciones Exteriores
Bogotá, D.C. 10/4/2000

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A todos aquellos presentes, saludos:

Yo, por la presente Certifico que el documento adjunto lleva el Sello de la Oficina de Marcas y Patentes, Departamento de Comercio de los Estados Unidos de America, y que dicho sello amerita plena fe y crédito.

En Testimonio de lo cual, Yo, Strobe Talbott, en mi calidad de Secretario de Estado, he fijado el Sello del Departamento de Estado y escribo mi nombre por parte del Funcionario Asistente de Autenticaciones, de dicho Departamento, en la Ciudad de Washington, en el Distrito de Columbia, el dieciseis de septiembre del año 2000.

Eduardo Calado
Eduardo Calado
SECRETARIO ENCARGADO
DE AUTENTICACIONES
DEL DEPARTAMENTO DE ESTADO

**Firma: Strobe Talbott
Secretario de Estado Encargado**

**Firma el Funcionario Encargado de
Autenticaciones del Departamento de Estado.**

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Oficina de Marcas y Patentes de los Estados Unidos

Agosto 21, 2000

**LA PRESENTE CERTIFICA QUE EL DOCUMENTO ADJUNTO ES UNA FIEL COPIA
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Autorizado Por:

COMISIONADO DE MARCAS Y PATENTES

FIRMA: H.L. JACKSON

Funcionario de certificaciones

Edward Calabak
DIRECTOR GENERAL
"TRADUCCION OFICIAL"
INGLES ESPANOL-INGLES
Rm 111, Febrero de 1998

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Fecha: 12/23/99

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Para el Honorable Comisionado de Marcas y Patentes. Favor presentar con el documento original adjunto una copia del mismo.

1- Nombre del (los)CEDENTE (s) :
Philip R. Kym, Tom von Gelderm, Benjamin C. Lane, John K. Pratt

Nombres adicionales de las Partes : ☐ Si ☒ No

2- Nombre y Dirección del (los) CESIONARIO (s):

Nombre: ABBOTT LABORATORIES
Dirección de sede: Patent and Trademark Department
D-377.AP6D

Dirección: Abbott Laboratories
100 Abbott Park Road

Ciudad: Abbott Park Estado: Illinois Código Postal: 60064-3500

Nombres adicionales de las Partes : ☐ Si ☒ No

3- Naturaleza de la Cesión:

☒ Traspaso

☐ Fusión

☐ Acuerdos de seguros

☐ Cambio de Razón Social

☐ Otros

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1-1021-3
hora de 12.0

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206

Fecha de celebración: 9/01/ 99 P.R. Kym

B.C. Lane

J. K. Pratt

9/15/ 99 T. von Gelderm

4. Número de Solicitud o Número de Patente (s) :

Si el documento se presenta con la solicitud, la fecha de registro de la ejecución del traspaso es:

A. Número de Solicitudde Patentes () y fecha de Registro:

TITULO: RECEPTORES ANTAGONISTAS DE GLUCOCORTICOIDES
PARA EL TRATAMIENTO DE DIABETES

Solicitud de Patente no. 388.251

Fecha de presentación: Septiembre 1, 1999

Se adjuntan números adicionales [] Si [x] No

5. NOMBRE Y DIRECCION A QUIEN SE DEBE ENVIAR LA RESPECTIVA
CORRESPONDENCIA:

Eduardo Palado
Eduardo Palado
DIRECTOR GENERAL
SECRETARÍA DE ECONOMÍA
ESTADOS UNIDOS MEXICANOS

219
207

NOMBRE:

STEVEN F. WEINSTOCK

DIRECCION :

Nombre: ABBOTT LABORATORIES

Dirección de sede: Patent and Trademark Department
D-377.AP6D

Dirección: Abbott Laboratories
100 Abbott Park Road

Ciudad: Abbott Park
3500

Estado: Illinois

Código Postal: 60064-

12/23/1999 JSHABA 08000037 010025 388251

6- Número de Solicitudes y Patentes incluidas: 1

7- Total Honorarios (37 CFR) 3.11).....\$40.00

Se adjuntan

[x] Se autoriza cobrar a la cuenta corriente

8- Número de Cuenta Corriente: 01-0025

)Se anexan duplicados de copia de la presente hoja en el caso de que
se efectue el pago por cuenta corriente)

Edward Caliendo
ABBOTT LABORATORIES
PATENT AND TRADEMARK DEPARTMENT
100 ABBOTT PARK ROAD
ABBOTT PARK, ILLINOIS 60064-3500

211
208

NO UTILIZAR ESTE ESPACIO

9. DECLARACION Y FIRMA:

Doy plena fe y reconocimiento de que la información anterior es fiel y verdadera y cualquier copia adjunta es una copia fiel y verdadera del documento original.

Nombre del firmante: Marc C. Bach, número de Registro: 34, 766

Ha firma de : Marc C. Bach

Fecha: 2/3/99

Número total de páginas incluyendo la cubierta, anexos y documentos [4]

Marc C. Bach
Firma de Marc C. Bach
-TR 101-1-10R 01/11/11
-GUS-ESCHOL-10-15
Rev. 541 febrero de 19.6

212
209

TRASPASO

CONSIDERANDO QUE, Philip R. Kym de Grayslake, IL, Tom Von Gelf de Richmond, IL, John K. Pratt de Kenosha, WI y Benjamin C. Lane de Libertyville, IL. a continuación llamados los "cedentes" son los autores del invento descrito a continuación en la solicitud de patentes de los Estados Unidos, llamada: "RECEPTORES ANTAGONISTAS DE GLUCOCORTICOIDE PARA EL TRATAMIENTO DE DIABETES", realizado por los "cedentes" en la misma fecha de este Traspaso, por medio del presente los cedentes autorizan y solicitan a los abogado(s) que aparecen en el listado del Poder que se presenta en este caso, para introducir en el parentesis (Número de Solicitud 388,251, presentado en 9/1/99) La fecha de registro y número de solicitud de dicha solicitud cuando se de a conocer.

CONSIDERANDO QUE, ABBOTT LABORATORIES, una empresa constituida y existente bajo las leyes de Illinois, la cual tiene sede principal de negocios en Abbott Park, Illinois 60064, a continuación llamados los "Cesionario" desean adquirir los derechos completos, títulos e interés de y para este invento y para la solicitud de patente anteriormente identificada y todas las patentes nacionales o extranjeras a obtenerse para dicho invento como a continuación.

Eduardo Salado Viqueira
Eduardo Salado Viqueira
-TRADUCCION OFICIAL-
INGLES-ESPAÑOL-INGLES
Rev 541 Febrero de 1996

~~213~~
210

Convenio; y que los cedentes

Edmundo Calles
Edmundo Calles
"TRANSMISOR OFICIAL"
V. CALLES CALLES
Rev. 511 - Febrero de 19.6

21A
211

cesionarios en la ejecución de las solicitudes de patentes mencionadas anteriormente, en la ejecución y realización de cualquier otra solicitud que el Cesionario decida seleccionar para complementar el invento anteriormente mencionado, conferir al Cesionario como exclusividad de título sobre otras mencionadas solicitudes y patentes, en el caso de que surja cualquier inconveniente que este relacionada con dicho invento, o en cualquier solicitud de patente o patente, y en asistir al Cesionario en la ejecución de cualquiera de los derechos que surjan en este traspaso; y que los Cedentes ejecuten y entreguen al cesionario cualquier y todos los documentos adicionales que necesiten los cedentes para realizar los terminos del convenio.

Caso No.: 6577.US.01

No. Serial:

F cha de Registro:

PATENTE

ROLLO: 010448

CUADRO: 0995

Eduardo Calado
Eduardo Calado Noguera
"TRADUCTOR OFICIAL"
Español-Inglés
Rev. 541 febrero de 1966

Por medio de la presente el Comisionado de Marcas y Patentes está autorizado y para expedir Patentes a los Cesionarios de acuerdo a los terminos establecidos del este convenio.

EN TESTIMONIO DE LO CUAL, los Cedentes han realizado el este acuerdo.

Fecha: 9/1/99	Firma: Philip R. Kym
Fecha: 9/15/99	Firma: Tom von Geldern
Fecha: 9/1/99	Firma: Benjamin C. Lane
Fecha: 9/1/99	John K. Pratt

Caso No. 6577.US.01

No. Serial:

Fecha de Registro:

PRESENTADO: 12/13/1999

Edward Paludo
EDWARD PALUDO
-TRADUCCION OFICIAL-
SECRETARÍA DE ECONOMÍA
1999-12-13



CONSULADO DE COLOMBIA
WASHINGTON, D.C.



212 213

No. 2444

EL CONSULADO DE COLOMBIA

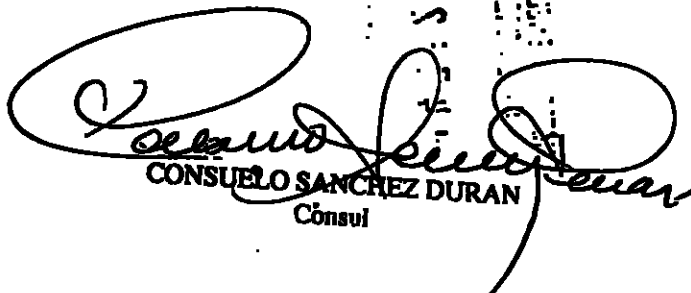
CERTIFICA:

Que es auténtica la firma de Patrick O. Hattchett
quien el día Septiembre 16 de 2000
desempeñaba las funciones de En Of. de Asst. Depto. de Estado
la cual aparece al pie de los documentos anexos relacionados con Registro de Planca.

Dado en Washington, D.C. a los veintidos (22) días del mes de Septiembre del año dos mil (2000)

Pagado Impuesto de Timbre 7=
Pagado Derecho Consular 15=
Total 22=

(El Consulado no asume ninguna
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documentos anexos)


CONSUELO SANCHEZ DURAN
Cónsul

MINISTERIO DE RELACIONES
EXTERIORES

NO SE ASUME
LA RESPONSABILIDAD DEL TEXTO

4471231
Consuelo Pandey
CUBA FUERA APARECE EN EL
BOCUNO DE LA PENNA
LAS FCHAS 1045

1000 OCT -4 P 12 29
M. J. 9
JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTÁ D.C.



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United States of America

0006-017

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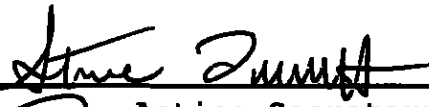
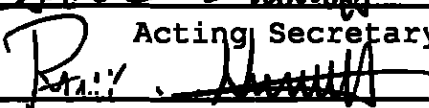


DEPARTMENT OF STATE

To all to whom these presents shall come, Greetings:

I Certify That the document hereunto annexed is under the Seal of the Patent and Trademark Office, Department of Commerce, United States of America, and that such Seal is entitled to full faith and credit.*

In testimony whereof, I, Strobe Talbott, Acting Secretary of State, have hereunto caused the seal of the Department of State to be affixed and my name subscribed by the Assistant Authentication Officer, of the said Department, at the city of Washington, in the District of Columbia, this sixteenth day of September, 2000.


Acting Secretary of State
By 
Assistant Authentication Officer,
Department of State

Issued pursuant to CHD IV, Stat. of
Sept. 15, 1789, 1 Stat. 68-69; 22
USC 2657; 22 USC 2651a; 5 USC
301; 28 USE 1733 et. seq.; 8 USC
1443(f); RULE 44 Federal Rules of
Civil Procedure.

*For the contents of the annexed document, the Department assumes no responsibility

This certificate is not valid if it is removed or altered in any way whatsoever

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THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

**UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office**

August 21, 2000

**THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE
RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON
December 13, 1999.**

**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**


**H. L. JACKSON
Certifying Officer**



12-23-1999

U.S. DEPARTMENT OF COMMERCE

Form PTO-1595

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12-13-99

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To the Honorable Commissioner of Patents and Trademarks. Please record the attached original documents of copy form of

1. Name of conveying party(ies): Philip R. Kym, Tom vonGeldern, Benjamin C. Lane, John K. Pratt Additional name(s) of conveying party(ies) ☐ Yes ☒ No 3. Nature of Conveyances ☒ Assignment ☐ Merger ☐ Security Agreement ☐ Change of Name ☐ Other Execution Date: 9/01/99 P.R. Kym 9/15/99 B.C. Lane J. K. Pratt T. vonGeldern	2. Name and address of receiving party(ies): Name: Abbott Laboratories Internal Address: Patent and Trademark Department D-377, AP6D Street Address: Abbott Laboratories 100 Abbott Park Road City: Abbott Park State: Illinois Zip: 60064-3500 Additional name(s) & address(es) attached? ☐ Yes ☒ No
---	--

4. Application number(s) or patent number(s)
If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s) and Filing Dates Title: GLUCOCORTICOID RECEPTOR ANTAGONISTS FOR TREATMENT OF DIABETES Patent Application No.: 388,251 Date of Filing: September 1, 1999	B. Patent No.(s) Additional numbers attached? ☐ Yes ☒ No
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5. Name and address of party to whom correspondence concerning document should be mailed: Name: Steven F. Weinstock Internal Address: Patent and Trademark Department D377, AP6D Street Address: Abbott Laboratories 100 Abbott Park Road City: Abbott Park State: Illinois Zip: 60064-4050	6. Total Number of applications and patents involved: 1 7. Total fee (37 CFR 3.41): \$40.00 Enclosed ☒ Authorized to be charged to deposit account 8. Deposit Account Number: 91-0925 (attached in a duplicate copy of this page if paying by deposit account)
--	--

12/23/1999 JSH/BJ
01 FF:541

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9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.
Mark C. Bach, Reg. No. 34,766
Name of Person Signing
Signature
Date 12/13/99
Total number of pages comprising cover sheet, attachments and document: 4

OMB No. 0301-0011 (rev. 0/94)
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Docket No. 657713LO1
Assistant Commissioner for Patents
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Washington D. C. 20231
Public burden reporting for this sample cover sheet is estimated about 30 minutes per document to be recorded, including time for reviewing the document and gathering the data needed, and completing and reviewing the sample cover sheet. Send comments regarding this burden estimate to the U. S. Patent and Trademark Office, Office of Information Systems, PK3-1002C, Washington D.C. 20231, and the Office of Management and Budget, Paperwork Reduction Project, (0301-0011), Washington, D.C. 20503

PATENT
REEL: 010448 FRAME: 0993

ASSIGNMENT

WHEREAS, Philip R. Kym of Grayslake, IL, Tom von Gelb of Richmond, IL, John K. Pratt of Kenosha, WI and Benjamin C. Lane of Libertyville, IL, hereinafter called the "Assignors", have made the invention described in the United States patent application entitled GLUCOCORTICOID RECEPTOR ANTAGONISTS FOR TREATMENT OF DIABETES executed by Assignors on the same date as this Assignment, Assignors hereby authorize and request the attorney(s) listed on the Power of Attorney filed in this case to insert here in parentheses (Application number 388,251, filed 9/1/99) the filing date and application number of said application when known;

WHEREAS, Abbott Laboratories, a corporation organized and existing under the laws of Illinois, having a place of business at Abbott Park, Illinois 60064, hereinafter called the "Assignee", desires to acquire the entire right, title and interest in and to the invention and to the patent application identified above, and all patents, foreign and domestic, which may be obtained for said invention, as set forth below;

NOW, THEREFORE, in consideration of the sum of One Dollar (\$1.00), and other valuable and legally sufficient consideration, *done and given* the receipt of which by the Assignors from the Assignee is hereby acknowledged, the Assignors have sold, assigned and transferred, and by these presents do sell, assign and transfer to the Assignee, the entire right, title and interest for the United States and

Docket No.: 6577.US.01
Serial No.: 388,251
Filing date: September 1, 1999

PATENT
REEL: 010448 FRAME: 0994

elsewhere in and to the invention and the patent application identified above, and any patents that may issue for said invention in the United States and elsewhere; together with the entire right, title and interest in and to said invention and all present applications, patents, utility models and designs therefor in all countries foreign to the United States, including the full right to claim for any such application all benefits and priority rights under any applicable convention; together with the entire right, title and interest in and to all continuations, divisions, renewals and extensions of any of the patent applications, patents, utility models and designs defined above; to have and to hold for sole and exclusive use and benefit of the Assignee, its successors and assigns, to the full end of the term or terms for all such patents.

The Assignors hereby covenant and agree, for both the Assignors and the Assignors' legal representative, that Assignors have the full right to convey the interest assigned by this Assignment; and that the Assignors will assist the Assignee in the prosecution of the patent applications identified above, in the making and prosecution of any other applications that the Assignee may elect to make covering the invention identified above, in vesting in the Assignee like exclusive title in and to all such other patent applications and patents, in the prosecution of any interference which may arise involving said invention, or any such patent application or patent, and in assisting Assignee in enforcement of any rights arising out of this Assignment; and that the Assignors will execute and deliver to the Assignee any and all additional papers which may be requested by the Assignee to carry out the terms of this Agreement.

Docket No.: 6577.US.01
Serial No.:
Filing date:

PATENT
REEL: 010448 FRAME: 0995

The Commissioner of Patents and Trademarks is hereby authorized and requested to issue patents to the Assignee in accordance with the terms of this Assignment.

IN TESTIMONY WHEREOF, the Assignors have executed this agreement.

DATED: 9/1/1999

Philip R. Kym

Philip R. Kym

DATED: 9/15/1999

Tom von Geldern

Tom von Geldern

DATED: 9/1/1999

Benjamin C. Lane

Benjamin C. Lane

DATED: 9-1-1999

John R. Pratt

John R. Pratt

Docket No.: 6577.US.01
Serial No.:
Filing date:

RECORDED: 12/13/1999

PATENT
REEL: 010448 FRAME: 0996