



No. 08-082662- -00003-0000

Fecha: 2010-04-27 10:57:30 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Fóllos: 109

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

Número del expediente: 08 082 662

Solicitante: DAIICHI SANKYO COMPANY, LIMITED.

**SOLICITUD
PUBLICADA**

Apoderado: EMILIO FERRERO

Título de la nueva creación o denominación del signo: COMPOSICION

FARMACEUTICA ANTICANCER QUE COMPRENDE UN COMPUESTO DE TIAZOLIDINDIONA

Gaceta: 612

③ **OPOSICIÓN PRESENTADA POR:**

SOLICITANTE

Nombre: PROCAPS S.A.

Dirección: CALLE 80 No. 78b-201

Nacionalidad o Domicilio: COLOMBIA
Lugar de Constitución: BARRANQUILLA

Teléfono: 371 99 00 Fax: 373 08 18
E-mail:

IDENTIFICACIÓN

C.C. ☐ NIT ☒

C.E. ☐ Otro ☐

Cual

Número 890.106.527-5

**REPRESENTANTE
O APODERADO**

Nombre: CIELO ANGELA PEÑA
RODRIGUEZ

Dirección: CARRERA 13 No. 119-95

Teléfono: (571)213 12 13 Fax: (571)612 19 79
E-mail: negocios@optimum-co.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual

Número 51.940.252 TP 82701

④ **FUNDAMENTOS DE LA OPOSICIÓN:**

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor: _____

Justificación: _____

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo
revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la
misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

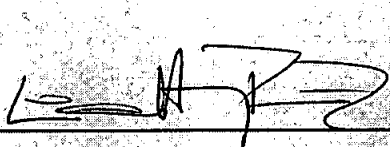
⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposicion.
- ☐ Documentos que acrediten el legitimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: CIELO ANGELA PEÑA RODRIGUEZ ✓FIRMA:  ✓

C.C. 51.940.252

TP. 82701

Señora Jefe,
DIVISIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Referencia : Expediente N° 08 082662
Asunto : Oposición a la solicitud de patente de Invención titulada
"COMPOSICIÓN FARMACÉUTICA ANTICÁNCER QUE
COMPRENDE UN COMPUESTO DE
TIAZOLIDINDIONA"
Solicitante : DAIICHI SANKYO COMPANY, LIMITED.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 612 del 29 de enero de 2010

Yo, *CIELO ANGELA PEÑA RODRIGUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. *82701* del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad *PROCAPS S.A.* conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "COMPOSICIÓN FARMACÉUTICA ANTICÁNCER QUE COMPRENDE UN COMPUESTO DE TIAZOLIDINDIONA", cuyo titular es DAIICHI SANKYO COMPANY, LIMITED,

y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular **TIAZOLIDINDIONA**. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 08 de agosto de 2008 reivindicando prioridad bajo la solicitud JP20060031791 del 2006-02-09; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 612 del 29 de enero de 2010, cuya publicación internacional corresponde a la WO2007/091622 del 16/08/2007.

2.2. La solicitud colombiana 08 082662 objeto de la presente oposición, se refiere a una composición farmacéutica anti cáncer para la profilaxis o el tratamiento de

cáncer gástrico, cáncer de colon, cáncer de pulmón, cáncer de mama, cáncer pancreático, cáncer de riñón, cáncer de próstata, meduloblastoma, rabdomiosarcoma, sarcoma de Ewing, liposarcoma, mieloma múltiple o leucemia, que comprende un compuesto de tiazolidindiona o una sal del mismo como ingrediente activo.

2.3. Con base en el artículo 14 de la Decisión 486 de la CAN que consagra lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la patentabilidad de la presente solicitud:

- D1: WO0195859 publicada el 20 de diciembre de 2001.
- D2: WO0205791 A2 publicada el 24 de enero de 2002.

2.4. Ahora bien, el documento D1, particularmente en la descripción revela unos compuestos de difeniletileno y derivados de los mismos con intermedios de tiazolidindiona u oxazolidindiona y que son útiles para tratar diabetes, hiperlipidemia y otras enfermedades relacionadas con la resistencia a la insulina, tales como enfermedad de las arterias coronarias y enfermedad vascular periférica, y también para 25 tratar o inhibir la inflamación o las enfermedades inflamatorias tales como artritis inflamatorias y enfermedades vasculares del colágeno, que son causadas por, por ejemplo, citoquinas o ciclo oxigenas as tales como TNF-alfa, 1L-1, 1L-6 y/o COX-2. Los compuestos también son útiles para

tratar o prevenir otras enfermedades mediadas por citoquinas y/o ciclooxigenasas, tales como cáncer.

2.5. Adicionalmente el documento D2, menciona particularmente en la descripción, y más adelante en las reivindicaciones 7 y 16 que la utilidad de inhibidores aromatasa, antagonistas de EGFR e inhibidores de EGF es bien reconocida en la terapia anti cáncer.

2.6. Considerando el documentos D1 el estado de la técnica más cercano a la invención tenemos que no es posible reconocer novedad ya que composiciones farmacéuticas anti cáncer, que comprenden un compuesto de tiazolidindiona o una sal del mismo, eran ampliamente conocidas a la fecha de prioridad.

2.7. Por lo tanto, la solicitud objeto de la presente oposición no puede comprender patente toda vez que no cumple con el requisito más importante, la NOVEDAD, dado que lo que pretende ya es ampliamente conocido en el arte anterior.

2.8. Tomando los documentos D1 y D2 no es posible reconocer altura inventiva, ya que sería obvio para un experto en la materia a partir del documento D1, apoyado en el hecho de que los compuestos ahí descritos tienen actividad anti cáncer y efectos sinérgicos en combinación con otras drogas anti cáncer y del documento D2, concebir una composición farmacéutica anti cáncer para la profilaxis o el tratamiento de cáncer gástrico, cáncer de colon, cáncer de pulmón, cáncer de mama, cáncer pancreático, cáncer de riñón, cáncer de próstata, meduloblastoma, rabdomiosarcoma, sarcoma de Ewing, liposarcoma, mieloma múltiple o leucemia, que comprende un compuesto de tiazolidindiona o una sal del mismo como ingrediente activo. Así entonces lo pretendido en la solicitud objeto de la presente oposición, carece de altura inventiva.

2.9. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08 082662 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.10. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.10.1. **CARECE DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."* A la fecha de prioridad, 09 de febrero de 2006 ya era conocido, pues como se demostró, era parte del arte anterior con base en los documentos D1 y D2, una composición farmacéutica anti cáncer, que comprende un compuesto de tiazolidindiona o una sal del mismo, sobre la cual busca protección en el capítulo reivindicatorio.

2.10.2. **CARENCIA DE ALTURA INVENTIVA.** Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."* A la fecha de prioridad, 09 de febrero de 2006, a partir del documento D1 por sí solo, o por la combinación de D1 y D2, puede llegar de manera evidente a una composición farmacéutica anti cáncer, que comprende un compuesto de tiazolidindiona o una sal del mismo

como ingrediente activo, sobre la cual busca protección en el capítulo reivindicatorio.

2.11. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14. *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.”*. La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.12. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y en consecuencia negar el registro a la solicitud de patente titulada **“COMPOSICIÓN FARMACÉUTICA ANTICÁNCER QUE COMPRENDE UN COMPUESTO DE TIAZOLIDINDIONA”**, cuyo titular es **DAIICHI SANKYO COMPANY, LIMITED**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 612 del 29 de enero de 2010.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: WO0195859 publicada el 20 de diciembre de 2001.
- D2: WO0205791 A2 publicada el 24 de enero de 2002.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **PROCAPS S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: WO0195859 publicada el 20 de diciembre de 2001.
 - D2: WO0205791 A2 publicada el 24 de enero de 2002.



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

CIELO ANGELA PEÑA RODRIGUEZ

C.C. 51'940.252 de Bogotá

T.P.A. 82701 del C.S. de la J.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-082662- -00003-0000

Fecha: 2010-04-27 10:57:30 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 109

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 32,632
FECHA : ABRIL 27 DE 2010

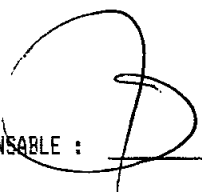
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	174684996	07/04/2010	590,000.00
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	174685000	07/04/2010	1,475,000.00

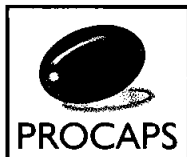
***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
12		MARCAS Y LEMAS COMERCIALES	295,000.00
		TOTAL :	\$ 295,000.00

SON: DOSCIENTOS NOVENTA Y CINCO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 82701 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 08 082.662, titulada "COMPOSICIÓN FARMACÉUTICA ANTICÁNCER QUE COMPRENDE UN COMPUESTO DE TIAZOLIDINDIONA", cuyo titular es **DAIICHI SANKYO COMPANY, LIMITED**, publicada en la gaceta No. 612 del 29 de enero de 2010.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 12 días del mes de abril de 2010.

PROCAPS S.A.

C.C. N° 16'251.923

NIT: 890.106.527-5

Representante Legal

Acepto:

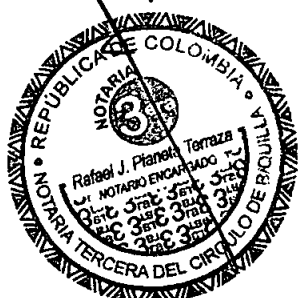
CIELO ANGELA PEÑA RODRIGUEZ

C.C. 51'940.252 de Bogotá

T.P.A. 82701 del C.S. de la J.

NOTARIA
NOTARIA TERCERA DEL CIRCULO DE BARRANQUILLA
DILIGENCIA DE RECONOCIMIENTO
Ante el Notario Tercero de Barranquilla se presento:
WALTER TANAKA TATEHAWA
identificado con: CC 16.251.923 *PACUIRA*
Y declaro que el contenido del anterior Documento es cierto
y suya la firma que lo respalda.
Barranquilla: 14 ABR. 2010

[Handwritten signature]





***** Pag. 1
CAMARA DE COMERCIO
DE BARRANQUILLA
10*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.

NIT: 890.106.527-5

EN JUNIO DE ESTE AÑO SE ELEGIRÁ JUNTA DIRECTIVA DE LA CÁMARA DE COMERCIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA QUINCENA DE MAYO. PARA INFORMACIÓN DETALLADA DIRIGIRSE A LA SEDE PRINCIPAL O COMUNICARSE AL SIGUIENTE TELEFONO: 3303718-3303716.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A. "PROCAPS S.A."

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. ---
NIT: 890.106.527-5.

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del libro respectivo, la sociedad antes mencionada ---
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A. ---

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del libro respectivo, la sociedad antes mencionada ---
cambio de razón social, por la denominación PROCAPS S.A. ---

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Número	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18
710	2009/05/05	Notaria 3 a. de Barranquilla	150,130	2009/06/30
1,054	2009/06/25	Notaria 3 a. de Barranquilla	150,130	2009/06/30

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:
DENOMINACION O RAZON SOCIAL:



***** Pag. 2
CAMARA DE COMERCIO
DE BARRANQUILLA
10*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5-----

PROCAPS S.A.-----

SIGLA: PROCAPS

DOMICILIO PRINCIPAL: Barranquilla

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.

C E R T I F I C A

Direccion para notificaciones judiciales:

CL 80 No 78 B 201.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a) La fabricacion, importacion y comercializacion de alimentos procesados y suplementos dietarios. b) La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, para uso y consumo humano y veterinario. c) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas para uso y consumo humano, animal y vegetal. d) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. e) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. f) La compra, venta, exportacion, fabricacion, importacion, distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. g) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos. h) Prestar los servicios de asesorias y consultoria en las areas administrativas,

***** C O N T I N U A *****

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de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, alimenticios, cosmeticos y farmaceuticos para uso humano, animal o industrial. i) Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, alimenticios, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables, comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles, designar representantes apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de sus obligaciones adquiridas por terceros o por sus socios para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.

CERTIFICA

CAPITAL	Nro Acciones	Valor Accion
Autorizado		
\$*****2,000,000,000	*****2,000,000	*****1,000
Suscrito		
\$*****1,229,071,000	*****1,229,071	*****1,000
Pagado		
\$*****1,229,071,000	*****1,229,071	*****1,000

CERTIFICA

ADMINISTRACION: La direccion y administracion de la sociedad correspondera a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transaccion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva.

***** CONTINUA *****



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La sociedad tendra un Presidente , quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultadas y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como

***** CONTINUA *****

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Representante legal por disposicion de la ley de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive, de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben
2. Minski Gontovnik Meyer
3. Minski Gontovnik Jose

CC.*****7,463,982

CC.*****7,461,324

CC.*****8,671,834

Suplentes

1. Minski Zirberblum Elliot

CC.*****72,219,541

***** C O N T I N U A *****



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C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
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2. Minski Deitel Daniel

3. Minski Sharon

PA *990,212,082,805

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente Minski Gontovnik Ruben	CC.*****7,463,982
Suplente del Presidente Minski Minski Abraham	CC.*****802,575
Vicepresidente Minski Gontovnik Meyer	CC.*****7,461,324
Suplente del vicepresidente Minski Gontovnik Jose	CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General. Uribe Ochoa Guillermo Luis	CC.*****70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente. Tanaka Tatekawa Walter	CC.*****16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a

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La Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Ppal. Vargas Pertuz Ana Isabel	CC.*****32,696,645

C E R T I F I C A

Que según Acta No. 151 del 31 de Marzo de 2009 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 30 de Julio de 2009 bajo el No. 151,129 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal. Duarte Díaz David	CC.*****73,115,965

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaría 2ª de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo,

y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, 3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, 3.507. Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, obrando como Presidente y Representante Legal de la sociedad C.I. NATURMEGA S.A., que obrando en su condición de Presidente y

Representante Legal de la sociedad PROCAPS S.A. el presidente debidamente facultado por los Estatutos Sociales y por el Maximo Organo Social, otorga los siguientes poderes: Otorgar poder general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con

las facultades que se transcriben a continuacion: a.- Para que representen a la sociedad PROCAPS S.A. ante todo tipo de autoridades administrativas y jurisdiccionales, en asuntos de naturaleza civil, laboral, comercial, penal, aduanera, cambiaria, tributaria, policiva, administrativa y fiscal. b.- Contestar y presentar demandas, requerimientos, recursos, pedir y aportar pruebas, recibir, notificarse, ejercer la accion de tutela, tramitar incidente de desacato, comparecer en los procesos que cursen contra la sociedad, allanarse en nombre de la sociedad en los asuntos que sean necesarios, transigir, desistir, sustituir, renunciar y reasumir el poder. c.- La facultad expresa de conciliar, por tanto pueden llegar a acuerdos conciliatorios, transaccionales, judiciales o extrajudiciales o extrajudiciales cualquiera que sea su cuantia, para lo cual las apoderadas deben aportar la autorizacion simple y escrita del Representante legal de la sociedad. d.- Podran presentar solicitudes de devolucion y/o compensacion de impuestos, ventas y rentas, recibir los pagos por



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las devoluciones y adelantar todo tramite o proceso administrativo ante la DIAN de tal forma que en ningun momento quede sin representacion legal de la sociedad. PODERES ESPECIALES: a.- Se confiere poder especial amplio y suficiente a las personas que se determinan seguidamente, que conforman el grupo A y B para, para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. Grupo A. WALTER NANAKA TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial amplio y suficiente al señor WILLIAM ALBERTO BARROS CERRA CC.No.8.715.941, para que en nombre y representacion de PROCAPS S.A., suscriban declaraciones cambiarias, aduaneras y tributarias a que este obligada la sociedad, en el giro normal de sus negocios y operaciones sociales, por tanto quedan facultados para firmarlas, como tambien los demas documentos relacionados con ellas, notificarse, aportar y solicitar las pruebas que sean necesarias. c.- Otorgar poder especial amplio y suficiente al señor MARLON TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS CERRA CC.No.8.715.941, para que en nombre y representacion de PROCAPS S.A. suscriban las declaraciones, reportes y cualquier documento relacionado con los tramites o registros de Comercio Exterior y o cualquier entidad del Estado que haga sus veces: d) Otorgar poder especial amplio y suficiente a la doctora CARMEN ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y representacion de PROCAPS S.A.; endosen los titulos valores de la sociedad hasta por la suma de UN MIL MILLONES DE PESOS (1.000.000.000.00) M.L. CUARTO: El representante legal de la sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta que la presente reforma fue aprobada por la Asamblea General Extraordinaria de Accionista de PROCAPS S.A., con observancia de las disposiciones legales y estatutarias.

C E R T I F I C A

Que por Escritura Pública No. 1,933 del 16 de Sep/bre de 2008, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Octubre de 2008

***** C O N T I N U A *****

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PROCAPS S.A. ---
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bajo el No. 3,748 del libro respectivo, ---
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, que
comparece en su condicion de Presidente y Representante Legal de la
Sociedad PROCAPS S.A., confiere por medio de este instrumento ---
publico Poder especial Amplio y Suficiente a la doctora MILENA ---
ESCAFFI PARDO, C.C. No. 32.758.420, para que en nombre y ---
representacion de PROCAPS S.A., suscriba declaraciones cambiarias
aduaneras y tributarias a que este obligada la sociedad en el giro
normal de sus negocios y operaciones sociales, por tanto queda ---
facultada para firmar, como tambien los demas documentos ---
relacionados con ellas, notificarse, aportar y solicitar las ---
pruebas que sean necesarias. ---

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores
de documentos referentes a reforma, disolución, liquidación o
nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 27 de Marzo de 2009.

La información sobre embargos de establecimiento se suministra en
Certificados de Matrícula, la de contratos sujetos a registro, en
Certificados Especiales.

C E R T I F I C A

Que los actos de registro aquí certificados quedan en firme cinco
días hábiles despues de la correspondiente inscripción, siempre
que, dentro de dicho término, no sean objeto de los recursos de
reposición ante esta entidad, y/o de apelación para ante la
Superintendencia de Industria y Comercio.

m. l. g. s.

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(25) Filing Language: English

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09/843,167 27 April 2001 (27.04.2001) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:

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Filed on	9 June 2000 (09.06.2000)
US	09/843,167 (CIP)
Filed on	27 April 2001 (27.04.2001)
US	09/785,554 (CIP)
Filed on	20 February 2001 (20.02.2001)

(71) Applicant (for all designated States except US): **CALYX THERAPEUTICS, INC.** [US/US]; 3525 Breakwater Avenue, Hayward, CA 94545 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **NEOGI, Partha** [IN/US]; 5091 Justin Terrace, Fremont, CA 94555 (US).

NAG, Bishwajit [US/US]; 34353 Eucalyptus Terrace, Fremont, CA 94555 (US). **MEDICHERLA, Satyanarayana** [US/US]; 10134 Tantau Avenue, Cupertino, CA 95014 (US). **DEY, Debendranath** [IN/US]; 34683 Agree Terrace, Fremont, CA 94555 (US).

(74) Agents: **KOKULIS, Paul, N.** et al.; Pillsbury Winthrop LLP, 1600 Tysons Boulevard, McLean, VA 22102 (US).

(81) Designated States (*national*): AE, AG, AI., AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

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



WO 01/95859 A2

(54) Title: NOVEL HETEROCYCLIC ANALOGS OF DIPHENYLETHYLENE COMPOUNDS

(57) Abstract: Novel diphenylethylene compounds and derivatives thereof containing thiazolidinedione or oxazolidinedione moieties are provided which are effective in lowering blood glucose level, serum insulin, triglyceride and free fatty acid levels in animal models of Type II diabetes. In contrast to previously reported thiazolidinedione compounds, known to lower leptin levels, the present compounds increase leptin levels and have no known liver toxicity. The compounds are disclosed as useful for a variety of treatments including the treatment of inflammation, inflammatory and immunological diseases, insulin resistance, hyperlipidemia, coronary artery disease, cancer and multiple sclerosis.

NOVEL HETEROCYCLIC ANALOGS OF
DIPHENYLETHYLENE COMPOUNDSCross Reference to Related Applications

5 This is a continuation-in-part of U.S. Patent Application Serial No.
09/785,554, filed February 20, 2001, which is a continuation-in-part of U.S.
Patent Application Serial No. 09/591,105, filed on June 9, 2000, which is a
continuation-in-part of Serial No. 09/287,237, filed on April 6, 1999, which is a
continuation-in-part of Serial No. 09/074,925, filed on May 8, 1998, the
10 disclosures of said earlier applications being incorporated herein by reference.

Background of the Invention

The present application is directed to novel compounds formed by
chemically coupling diphenylethylene compounds and derivatives thereof with
thiazolidine or oxazolidine intermediates. These compounds are effective for
15 providing a variety of useful pharmacological effects. For example, the
compounds are useful in lowering blood glucose, serum insulin and
triglyceride levels in animal models of type II diabetes. Surprisingly, these
compounds have been found to increase the leptin level and have no liver
toxicity.

20 Furthermore, these compounds are useful for treatment of disorders
associated with insulin resistance, such as polycystic ovary syndrome, as well
as hyperlipidemia, coronary artery disease and peripheral vascular disease,
and for the treatment of inflammation and immunological diseases, particularly
those mediated by cytokines and cyclooxygenase such as TNF-alpha, IL-1,
25 IL-6 and/or COX-2.

The causes of type I and type II diabetes are yet unknown, although
both genetics and environment seem to be major factors. Insulin dependent
type I and non-insulin dependent type II are the types which are known. Type
I is an autoimmune disease in which the responsible autoantigen is still

unknown. Patients of type I need to take insulin parenterally or subcutaneously to survive. However, type II diabetes, the more common form, is a metabolic disorder resulting from the body's inability to make a sufficient amount of insulin or to properly use the insulin that is produced.

5 Insulin secretion and insulin resistance are considered the major defects, however, the precise genetic factors involved in the mechanism remain unknown.

Patients with diabetes usually have one or more of the following defects:

- 10 Less production of insulin by the pancreas;
- Over secretion of glucose by the liver;
- Independent of the glucose uptake by the skeletal muscles;
- Defects in glucose transporters, desensitization of insulin receptors;
- and
- 15 Defects in the metabolic breakdown of polysaccharides.

Other than the parenteral or subcutaneous application of insulin, there are about 4 classes of oral hypoglycemic agents used.

Class	Approved Drugs	Mechanisms of	Limitations
Sulfonylurea	4 (1st generation) and 2 (2nd generation)	acts on pancreas to release more insulin	development of resistance
Biguanides	Metformin	reduces glucose production by liver; improves insulin sensitivity	liver problems, lactic acidosis
Alpha`-glucosidase inhibitor	Acarbose	interferes with digestive process; reduces glucose absorption	only useful at post-prandial level

Thiazolidinedione	Troglitazone (withdrawn) rosiglitazone pioglitazone	reduce insulin resistancy	"add-on" with insulin; not useful for people with heart and liver disease
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As is apparent from the above table, each of the current agents available for use in treatment of diabetes has certain disadvantages.

Accordingly, there is a continuing interest in the identification and

- 5 development of new agents, particularly, water soluble agents which can be orally administered, for use in the treatment of diabetes.

The thiazolidinedione class listed in the above table has gained more widespread use in recent years for treatment of type II diabetes, exhibiting particular usefulness as insulin sensitizers to combat "insulin resistance", a
10 condition in which the patient becomes less responsive to the effects of insulin. However, the known thiazolidinediones are not effective for a significant portion of the patient population. In addition, the first drug in this class to be approved by the FDA, troglitazone, was withdrawn from the market due to problems of liver toxicity. Thus, there is a continuing need for
15 nontoxic, more widely effective insulin sensitizers.

Pharmaceutical compositions and methods utilizing thiazolidinediones are described in U.S. Patent Nos. 6,133,295; 6,133,293; 6,130,216; 6,121,295; 6,121,294; 6,117,893; 6,114,526; 6,110,951; 6,110,948; 6,107,323; 6,103,742; 6,080,765; 6,046,222; 6,046,202; 6,034,110;
20 6,030,973; RE36,575; 6,011,036; 6,011,031; 6,008,237; 5,990,139; 5,985,884; 5,972,973 and others.

As indicated above, the present invention is also concerned with treatment of immunological diseases or inflammation, notably such diseases as are mediated by cytokines or cyclooxygenase. The principal elements of
25 the immune system are macrophages or antigen-presenting cells, T cells and B cells. The role of other immune cells such as NK cells, basophils, mast cells and dendritic cells are known, but their role in primary immunologic

disorders is uncertain. Macrophages are important mediators of both inflammation and providing the necessary "help" for T cell stimulation and proliferation. Most importantly macrophages make IL 1, IL 12 and TNF α all of which are potent pro-inflammatory molecules and also provide help for T cells.

5 In addition, activation of macrophages results in the induction of enzymes, such as cyclooxygenase II (COX-2), inducible nitric oxide synthase (iNOS) and production of free radicals capable of damaging normal cells. Many factors activate macrophages, including bacterial products, superantigens and interferon gamma (IFN γ). It is believed that phosphotyrosine kinases (PTKs) and other undefined cellular kinases are involved in the activation process.

10 Macrophages take up and break down antigens into small fragments. These fragments then associate with the major histocompatibility complex II (MHC II). This complex of antigen fragments and MHC II is recognized by the T cell receptor. In association with appropriate co-stimulatory signals this
15 receptor-ligand interaction leads to the activation and proliferation of T cells. Depending on the route of administration of antigen, their dose and the conditions under which macrophages are activated, the immune response can result in either B cell help and antibody production or on the development of cell mediated response. Since macrophages are sentinel to the development
20 of an immune response, agents that modify their function, specifically their cytokine secretion profile, are likely to determine the direction and potency of the immune response.

Cytokines are molecules secreted by immune cells that are important in mediating immune responses. Cytokine production may lead to the
25 secretion of other cytokines, altered cellular function, cell division or differentiation. Inflammation is the body's normal response to injury or infection. However, in inflammatory diseases such as rheumatoid arthritis, pathologic inflammatory processes can lead to morbidity and mortality. The cytokine tumor necrosis factor-alpha (TNF-alpha) plays a central role in the
30 inflammatory response and has been targeted as a point of intervention in inflammatory disease. TNF-alpha is a polypeptide hormone released by

activated macrophages and other cells. At low concentrations, TNF-alpha participates in the protective inflammatory response by activating leukocytes and promoting their migration to extravascular sites of inflammation (Moser et al., J Clin Invest, 83:444-55, 1989). At higher concentrations, TNF-alpha can

5 act as a potent pyrogen and induce the production of other pro-inflammatory cytokines (Haworth et al., Eur J Immunol, 21:2575-79, 1991; Brennan et al., Lancet, 2:244-7, 1989). TNF-alpha also stimulates the synthesis of acute-phase proteins. In rheumatoid arthritis, a chronic and progressive inflammatory disease affecting about 1% of the adult U.S. population, TNF-

10 alpha mediates the cytokine cascade that leads to joint damage and destruction (Arend et al., Arthritis Rheum, 38:151-60, 1995). Inhibitors of TNF-alpha, including soluble TNF receptors (etanercept) (Goldenberg, Clin Ther, 21:75-87, 1999) and anti-TNF-alpha antibody (infliximab) (Luong et al., Ann Pharmacother, 34:743-60, 2000), have recently been approved by the U.S.

15 Food and Drug Administration (FDA) as agents for the treatment of rheumatoid arthritis.

Elevated levels of TNF-alpha have also been implicated in many other disorders and disease conditions, including cachexia (Fong et al., Am J Physiol, 256:R659-65, 1989), septic shock syndrome (Tracey et al., Proc Soc

20 Exp Biol Med, 200:233-9, 1992), osteoarthritis (Venn et al., Arthritis Rheum, 36:819-26, 1993), inflammatory bowel disease such as Crohn's disease and ulcerative colitis (Murch et al., Gut, 32:913-7, 1991), Behcet's disease (Akoglu et al., J Rheumatol, 17:1107-8, 1990), Kawasaki disease (Matsubara et al., Clin Immunol Immunopathol, 56:29-36, 1990), cerebral malaria (Grau et al., N

25 Engl J Med, 320:1586-91, 1989), adult respiratory distress syndrome (Millar et al., Lancet 2:712-4, 1989), asbestosis and silicosis (Bissonnette et al., Inflammation, 13:329-39, 1989), pulmonary sarcoidosis (Baughman et al., J Lab Clin Med, 115:36-42, 1990), asthma (Shah et al., Clin Exp Allergy, 25:1038-44, 1995), AIDS (Dezube et al., J Acquir Immune Defic Syndr,

30 5:1099-104, 1992), meningitis (Waage et al., Lancet, 1:355-7, 1987), psoriasis (Oh et al., J Am Acad Dermatol, 42:829-30, 2000), graft versus host reaction

(Nestel et al., J Exp Med, 175:405-13, 1992), multiple sclerosis (Sharief et al., N Engl J Med, 325:467-72, 1991), systemic lupus erythematosus (Maury et al., Int J Tissue React, 11:189-93, 1989), diabetes (Hotamisligil et al., Science, 259:87-91, 1993) and atherosclerosis (Bruunsgaard et al., Clin Exp Immunol, 121:255-60, 2000).

It can be seen from the references cited above that inhibitors of TNF-alpha are potentially useful in the treatment of a wide variety of diseases. Compounds that inhibit TNF-alpha have been described in U.S. Pat. Nos. 6,090,817; 6,080,763; 6,080,580; 6,075,041; 6,057,369; 6,048,841; 6,046,319; 6,046,221; 6,040,329; 6,034,100; 6,028,086; 6,022,884; 6,015,558; 6,004,974; 5,990,119; 5,981,701; 5,977,122; 5,972,936; 5,968,945; 5,962,478; 5,958,953; 5,958,409; 5,955,480; 5,948,786; 5,935,978; 5,935,977; 5,929,117; 5,925,636; 5,900,430; 5,900,417; 5,891,883; 5,869,677 and others.

Interleukin-6 (IL-6) is another pro-inflammatory cytokine that exhibits pleiotropy and redundancy of action. IL-6 participates in the immune response, inflammation and hematopoiesis. It is a potent inducer of the hepatic acute phase response and is a powerful stimulator of the hypothalamic-pituitary-adrenal axis that is under negative control by glucocorticoids. IL-6 promotes the secretion of growth hormone but inhibits release of thyroid stimulating hormone. Elevated levels of IL-6 are seen in several inflammatory diseases, and inhibition of the IL-6 cytokine subfamily has been suggested as a strategy to improve therapy for rheumatoid arthritis (Carroll et al., Inflamm Res, 47:1-7, 1998). In addition, IL-6 has been implicated in the progression of atherosclerosis and the pathogenesis of coronary heart disease (Yudkin et al., Atherosclerosis, 148:209-14, 1999). Overproduction of IL-6 is also seen in steroid withdrawal syndrome, conditions related to deregulated vasopressin secretion, and osteoporosis associated with increased bone resorption, such as in cases of hyperparathyroidism and sex-steroid deficiency (Papanicolaou et al., Ann Intern Med, 128:127-37, 1998).

Since excessive production of IL-6 is implicated in several disease states, it is highly desirable to develop compounds that inhibit IL-6 secretion. Compounds that inhibit IL-6 have been described in U.S. Pat. Nos. 6,004,813; 5,527,546 and 5,166,137.

5 Cyclooxygenase is an enzyme that catalyzes a rate-determining step in the biosynthesis of prostaglandins, which are important mediators of inflammation and pain. The enzyme occurs as at least two distinct isomers, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). The COX-1 isomer is constitutively expressed in the gastric mucosa, platelets and other
10 cells and is involved in the maintenance of homeostasis in mammals, including protecting the integrity of the digestive tract. The COX-2 isomer, on the other hand, is not constitutively expressed but rather is induced by various agents, such as cytokines, mitogens, hormones and growth factors. In particular, COX-2 is induced during the inflammatory response (DeWitt DL,
15 Biochim Biophys Acta, 1083:121-34, 1991; Seibert et al., Receptor, 4:17-23, 1994.). Aspirin and other conventional non-steroid anti-inflammatory drugs (NSAIDs) are non-selective inhibitors of both COX-1 and COX-2. They can be effective in reducing inflammatory pain and swelling, but since they hamper the protective action of COX-1, they produce undesirable side effects of
20 gastrointestinal pathology. Therefore, agents that selectively inhibit COX-2 but not COX-1 are preferable for treatment of inflammatory diseases. Recently, a diarylpyrazole sulfonamide (celecoxib) that selectively inhibits COX-2 has been approved by the FDA for use in the treatment of rheumatoid arthritis (Luong et al., Ann Pharmacother, 34:743-60, 2000; Penning et al., J Med
25 Chem, 40:1347-65, 1997). COX-2 is also expressed in many cancers and precancerous lesions, and there is mounting evidence that selective COX-2 inhibitors may be useful for treating and preventing colorectal, breast and other cancers (Taketo MM, J Natl Cancer Inst, 90:1609-20, 1998; Fournier et al., J Cell Biochem Suppl, 34:97-102, 2000; Masferrer et al., Cancer
30 Res., 60:1306-11, 2000). In 1999 celecoxib was approved by the FDA as an

adjunct to usual care for patients with familial adenomatous polyposis, a condition which, left untreated, generally leads to colorectal cancer.

Compounds that selectively inhibit COX-2 have been described in U.S. Pat. Nos. 5,344,991; 5,380,738; 5,434,178; 5,466,823; 5,474,995; 5,510,368; 5,521,207; 5,521,213; 5,536,752; 5,550,142; 5,552,422; 5,604,260; 5,639,780; 5,643,933; 5,677,318; 5,691,374; 5,698,584; 5,710,140; 5,733,909; 5,789,413; 5,811,425; 5,817,700; 5,849,943; 5,859,257; 5,861,419; 5,905,089; 5,922,742; 5,925,631; 5,932,598; 5,945,539; 5,968,958; 5,981,576; 5,994,379; 5,994,381; 6,001,843; 6,002,014; 6,004,950; 6,004,960; 6,005,000; 6,020,343; 6,034,256; 6,046,191; 6,046,217; 6,057,319; 6,071,936; 6,071,954; 6,077,850; 6,077,868; 6,077,869 and 6,083,969.

The cytokine IL-1 beta also participates in the inflammatory response. It stimulates thymocyte proliferation, fibroblast growth factor activity, and the release of prostaglandin from synovial cells.

Elevated or unregulated levels of the cytokine IL-1 beta have been associated with a number of inflammatory diseases and other disease states, including but not limited to adult respiratory distress syndrome (Meduri et al, Chest 107:1062-73, 1995), allergy (Hastie et al, Cytokine 8:730-8, 1996), Alzheimer's disease (O'Barr et al, J Neuroimmunol 109:87-94, 2000), anorexia (Laye et al, Am J Physiol Regul Integr Comp Physiol 279:R93-8, 2000), asthma (Sousa et al, Thorax 52:407-10, 1997), atherosclerosis (Dewberry et al, Arterioscler Thromb Vasc Biol 20:2394-400, 2000), brain tumors (Ilyin et al, Mol Chem Neuropathol 33:125-37, 1998), cachexia (Nakatani et al, Res Commun Mol Pathol Pharmacol 102:241-9, 1998), carcinoma (Ikemoto et al, Anticancer Res 20:317-21, 2000), chronic arthritis (van den Berg et al, Clin Exp Rheumatol 17:S105-14, 1999), chronic fatigue syndrome (Cannon et al, J Clin Immunol 17:253-61, 1997), CNS trauma (Herx et al, J Immunol 165:2232-9, 2000), epilepsy (De Simoni et al, Eur J Neurosci 12:2623-33, 2000), fibrotic lung diseases (Pan et al, Pathol Int 46:91-9, 1996), fulminant hepatic failure (Sekiyama et al, Clin Exp Immunol 98:71-7, 1994), gingivitis

(Biesbrock et al, Monogr Oral Sci 17:20-31, 2000), glomerulonephritis (Kluth et al, J Nephrol 12:66-75, 1999), Guillain-Barre syndrome (Zhu et al, Clin Immunol Immunopathol 84:85-94, 1997), heat hyperalgesia (Opree et al, J Neurosci 20:6289-93, 2000), hemorrhage and endotoxemia (Parsey et al, J Immunol 160:1007-13, 1998), inflammatory bowel disease (Olson et al, J Pediatr Gastroenterol Nutr 16:241-6, 1993), leukemia (Estrov et al, Leuk Lymphoma 24:379-91, 1997), leukemic arthritis (Rudwaleit et al, Arthritis Rheum 41:1695-700, 1998), systemic lupus erythematosus (Mao et al, Autoimmunity 24:71-9, 1996), multiple sclerosis (Martin et al, J Neuroimmunol 61:241-5, 1995), osteoarthritis (Hernvann et al, Osteoarthritis Cartilage 4:139-42, 1996), osteoporosis (Zheng et al, Maturitas 26:63-71, 1997), Parkinson's disease (Bessler et al, Biomed Pharmacother 53:141-5, 1999), POEMS syndrome (Gherardi et al, Blood 83:2587-93, 1994), pre-term labor (Dudley, J Reprod Immunol 36:93-109, 1997), psoriasis (Bonifati et al, J Biol Regul Homeost Agents 11:133-6, 1997), reperfusion injury (Clark et al, J Surg Res 58:675-81, 1995), rheumatoid arthritis (Seitz et al, J Rheumatol 23:1512-6, 1996), septic shock (van Deuren et al, Blood 90:1101-8, 1997), systemic vasculitis (Brooks et al, Clin Exp Immunol 106:273-9, 1996), temporal mandibular joint disease (Nordahl et al, Eur J Oral Sci 106:559-63, 1998), tuberculosis (Tsao et al, Tuber Lung Dis 79:279-85, 1999), viral rhinitis (Roseler et al, Eur Arch Otorhinolaryngol Suppl 1:S61-3, 1995), and pain and/or inflammation resulting from strain, sprain, trauma, surgery, infection or other disease processes.

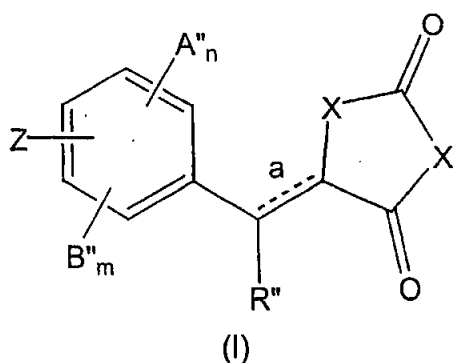
Since overproduction of IL-1 beta is associated with numerous disease conditions, it is desirable to develop compounds that inhibit the production or activity of IL-1 beta. Methods and compositions for inhibiting IL-1 beta are described in U.S. Patent Nos. 6,096,728; 6,090,775; 6,083,521; 6,036,978; 6,034,107; 6,034,100; 6,027,712; 6,024,940; 5,955,480; 5,922,573; 5,919,444; 5,905,089; 5,874,592; 5,874,561; 5,874,424; 5,840,277; 5,837,719; 5,817,670; 5,817,306; 5,792,778; 5,780,513; 5,776,979; 5,776,954; 5,767,064; 5,747,444; 5,739,282; 5,731,343; 5,726,148;

5,684,017; 5,683,992; 5,668,143; 5,624,931; 5,618,804; 5,527,940;
5,521,185; 5,492,888; 5,488,032 and others.

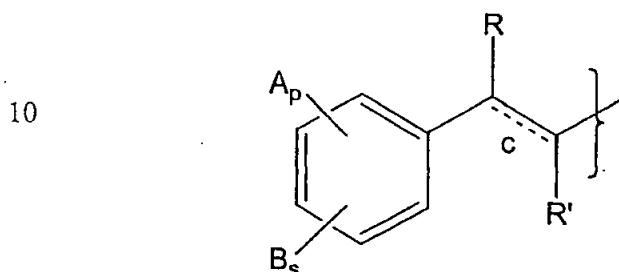
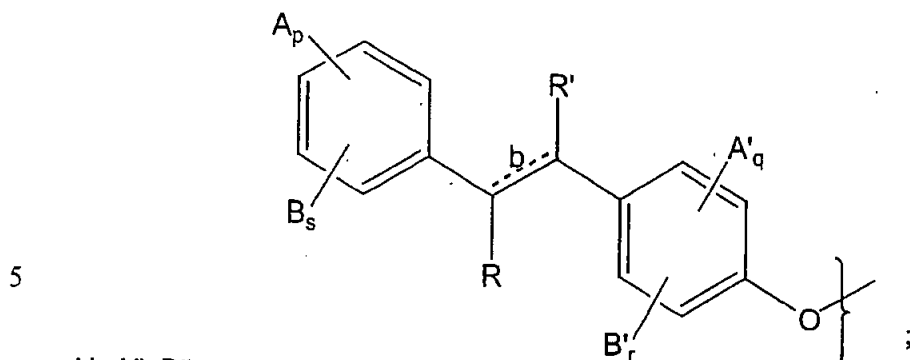
It will be appreciated from the foregoing that, while there have been extensive prior efforts to provide compounds for inhibiting, for example, TNF-
5 alpha, IL-1, IL-6, COX-2 or other agents considered responsible for immune response, inflammation or inflammatory diseases, e.g. arthritis, there still remains a need for new and improved compounds for effectively treating or inhibiting such diseases. A principal object of the invention is to provide compounds which are effective for such treatments as well as for the
10 treatment of, for example, insulin resistance, hyperlipidemia, coronary heart disease, multiple sclerosis and cancer.

Summary of the Invention

In one aspect of the invention, compounds of the following formula I
15 are provided:



wherein Z is



15 wherein n, m, q and r are independently integers from zero to 4 provided that $n + m \leq 4$, and $q + r \leq 4$; p and s are independently integers from zero to 5 provided that $p + s \leq 5$; a, b and c are double bonds which may be present or absent; when present, the double bonds may be in the E or Z configuration and, when absent, the resulting stereocenters can have the R- or S-
20 configuration;

R, R' and R'' are independently H, C₁-C₂₀ linear or branched alkyl, C₂-C₂₀ linear or branched alkenyl, -CO₂Z' where Z' is H, sodium, potassium, or other pharmaceutically acceptable counter-ion such as calcium, magnesium,
25 ammonium, tromethamine, and the like; -CO₂R''', -NH₂, -NHR''', -NR₂'', -OH, -OR''', halo, substituted C₁-C₂₀ linear or branched alkyl or substituted C₂-C₂₀ linear or branched alkenyl, wherein R''' is C₁-C₂₀ linear or branched alkyl or linear or branched alkenyl;

A, A' and A'' are independently H, C₁-C₂₀ acylamino;
30 C₁-C₂₀ acyloxy; C₁-C₂₀ alkanoyl;
C₁-C₂₀ alkoxycarbonyl; C₁-C₂₀ alkoxy;

C₁-C₂₀ alkylamino; C₁-C₂₀ alkylcarboxylamino; carboxyl; cyano;
halo; hydroxy;

B, B' and B'' are independently H;

C₁-C₂₀ acylamino; C₁-C₂₀ acyloxy; C₁-C₂₀ alkanoyl;

5 C₁-C₂₀ alkenoyl; C₁-C₂₀ alkoxycarbonyl;

C₁-C₂₀ alkoxy; C₁-C₂₀ alkylamino;

C₁-C₂₀ alkylcarboxylamino; aroyl, aralkanoyl; carboxyl; cyano; halo;
hydroxy;

or A and B together, or A' and B' together, or A'' and B'' together, may be
10 joined to form a methylenedioxy or ethylenedioxy group;

X, X' are independently -NH, -NR'', O or S.

These compounds are useful for treating diabetes, hyperlipidemia and
other diseases linked to insulin resistance, such as coronary artery disease
and peripheral vascular disease, and also for treating or inhibiting
15 inflammation or inflammatory diseases such as inflammatory arthritides and
collagen vascular diseases, which are caused by, for example, cytokines or
cyclooxygenase such as TNF-alpha, IL-1, IL-6 and/or COX-2. The
compounds are also useful for treating or preventing other diseases mediated
by cytokines and/or cyclooxygenase, such as cancer.

20 Accordingly, the invention also provides a method of treating diabetes
and related diseases comprising the step of administering to a subject
suffering from a diabetic or related condition a therapeutically effective
amount of a compound of Formula I. Additionally, the invention provides a
method of treating inflammation or inflammatory diseases or diseases
25 mediated by cytokines and/or cyclooxygenase by administering to a subject in
need of such treatment an effective amount of a compound according to
Formula I. Other uses will also be evident from this specification.

Pharmaceutical compositions containing a therapeutically effective
amount of one or more compounds according to Formula I together with a
30 pharmaceutically or physiologically acceptable carrier, for use in the
treatments contemplated herein, are also provided.

Brief Description of the Drawings

FIGS. 1A and 1B show graphs of the blood glucose levels and body weights, respectively, of db/db (spontaneous diabetic) male mice given a compound according to the invention of a period of 15 days.

5 FIGS. 2A and 2B show graphs of the blood glucose levels and body weights of ob/ob (genetically obese and spontaneously diabetic) male mice given a compound according to the invention over a period of 15 days.

10 FIGS. 3A and 3B with graphs of blood glucose levels of db/db mice and ob/ob mice, respectively, given a compound according to the invention over a period of 20-25 days.

FIG. 4 shows a graph of blood glucose level in db/db male mice over 72 hours following a dosage of the compound.

15 FIGS. 5A, 5B, 5C and 5D show graphs of the triglyceride levels, free fatty acid levels, glyc-Hb levels and leptin levels in serum of the db/db mice treated with a compound according to the present invention.

FIGS. 6A, 6B, 6C and 6D are graphs showing the serum insulin levels, triglyceride levels, free fatty acid levels and Glyc-Hb levels of serum of ob/ob mice treated with a compound according to the present invention.

20 FIGS. 7A and 7B show the assays of liver enzymes in mice 21 days after treatment with a compound according to the invention.

FIG. 8 shows glucose uptake in 3T3-L1 cells for a compound of the invention.

FIG. 9 shows a graph of the comparison of a compound of the invention with rosiglitazone for inhibition of LPS-induced TNF production.

25 FIG. 10 is a graph of the comparison of a compound of the invention with rosiglitazone for inhibition of LPS-induced IL-6 production.

FIG. 11 is a graph of the comparison of a compound of the invention with rosiglitazone for inhibition of LPS-induced IL-1-beta production.

30 FIGS. 12A and 12B show a comparison of a compound of the invention (FIG. 12A) with rosiglitazone (FIG. 12B) for inhibition of LPS-induced COX-2 activity.

FIGS. 13A, 13B, 13C and 13D illustrate the suppression of collagen-induced arthritis by using a compound according to the invention.

FIG. 14 illustrates the suppression of experimental allergic encephalomyelitis (EAE) by using a compound according to the invention.

5

Description of the Preferred Embodiments

A preferred compound according to Formula I is 5-(4-(4-(1-carbomethoxy)-2-(3,5-dimethoxyphenyl)-ethenyl)-phenoxy)-benzyl)-2,4-thiazolidinedione, hereinafter referred to as Compound VIII. However, it will
10 be appreciated that the invention also contemplates the provision and use of other compounds according to Formula I.

The compounds according to the present invention may be combined with a physiologically acceptable carrier or vehicle to provide a pharmaceutical composition, such as, lyophilized powder in the form of tablet
15 or capsule with various fillers and binders. The effective dosage of a compound in the composition can be widely varied as selected by those of ordinary skill in the art and may be empirically determined.

As earlier indicated, the compounds of the invention are useful for the treatment of diabetes, characterized by the presence of elevated blood
20 glucose levels, that is, hyperglycemic disorders such as diabetes mellitus, including both type I and II diabetes, as well as other hyperglycemic related disorders such as obesity, increased cholesterol, hyperlipidemia such as hypertriglyceridemia, kidney related disorders and the like. The compounds are also useful for the treatment of disorders linked to insulin resistance
25 and/or hyperinsulinemia, which include, in addition to diabetes, hyperandrogenic conditions such as polycystic ovary syndrome (Ibanez et al., J. Clin Endocrinol Metab, 85:3526-30, 2000; Taylor A.E., Obstet Gynecol Clin North Am, 27:583-95, 2000), coronary artery disease such as atherosclerosis and vascular restenosis, and peripheral vascular disease. Additionally, the
30 compounds of the present invention are also useful for the treatment of inflammation and immunological diseases that include those mediated by

signaling pathways linked to pro-inflammatory cytokines, such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, psoriasis, and contact and atopic dermatitis.

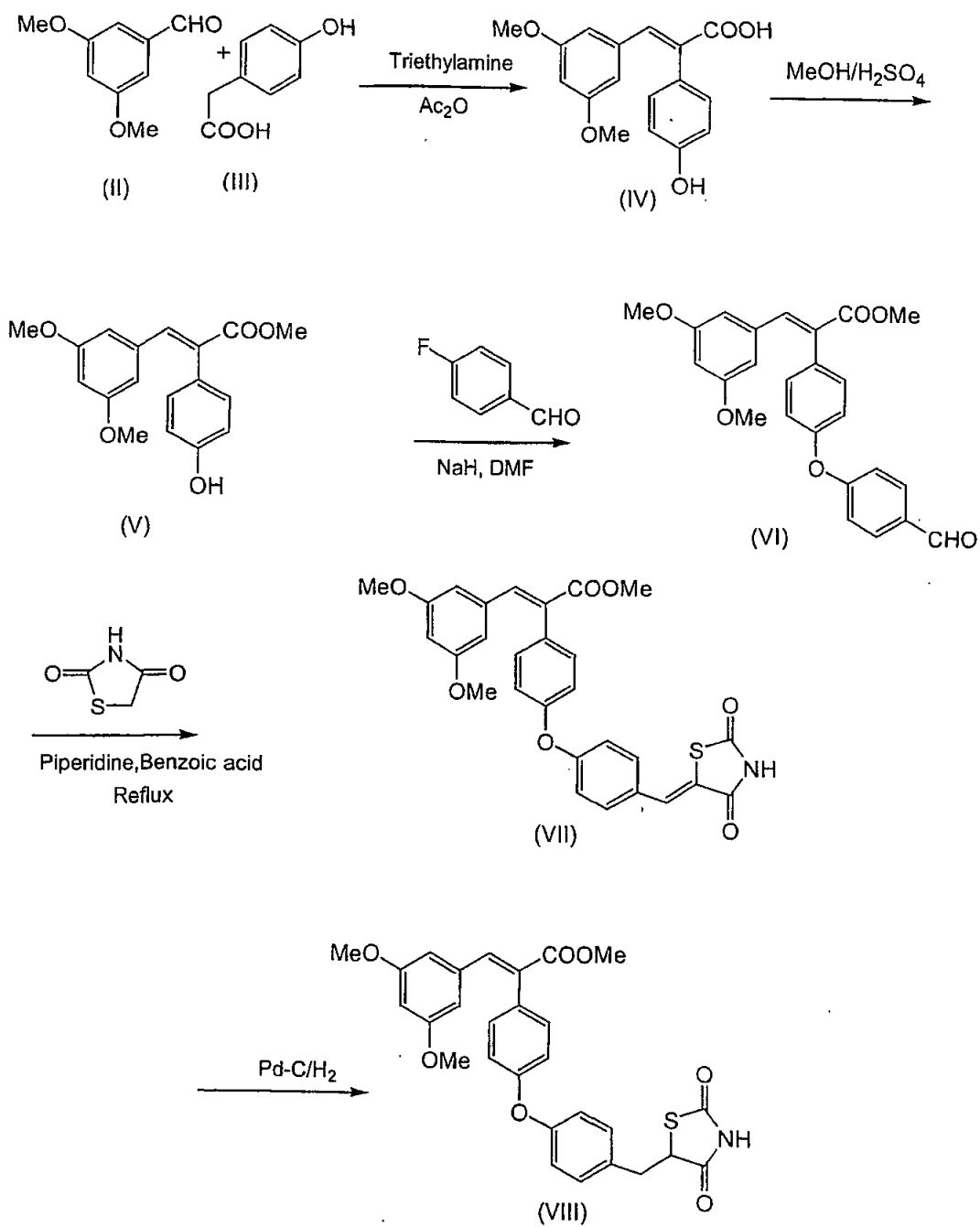
By "treatment", it is meant that the compounds of the invention are administered in an amount which is at least sufficient to, for example, reduce the blood glucose level in a patient suffering from hyperglycemic disorder or to inhibit or prevent the development of pro-inflammatory cytokine or like responses in a patient suffering from inflammatory or immunological disease. In the case of diabetes, the compound is usually administered in the amount sufficient to reduce the blood glucose level, free fatty acid level, cholesterol level, and the like to an acceptable range, where an acceptable range means + or - 10%, and usually + or - 5% of the normal average blood glucose level and like level of the subject, or sufficient to alleviate the symptoms and/or reduce the risk of complications associated with elevated levels of these parameters. A variety of subjects may be treated with the present compounds to reduce blood glucose levels such as livestock, wild or rare animals, pets, as well as humans. The compounds may be administered to a subject suffering from hyperglycemic disorder using any convenient administration technique, including intravenous, intradermal, intramuscular, subcutaneous, oral and the like. However, oral daily dosage is preferred. The dosage delivered to the host will necessarily depend upon the route by which the compound is delivered, but generally ranges from about 0.1-500 mg/kg human body weight or typically from about 1 to 50 mg/kg human body weight. Generally similar types of administration and dosages are also contemplated when the compounds of the invention are used to treat inflammatory or immunological disease.

The compounds of this invention may be used in formulations using acceptable pharmaceutical vehicles for enteral, or parenteral, administration, such as, for example, water, alcohol, gelatin, gum arabic, lactose, amylase, magnesium stearate, talc, vegetable oils, polyalkylene glycol, and the like. The compounds can be formulated in solid form, e.g., as tablets, capsules,

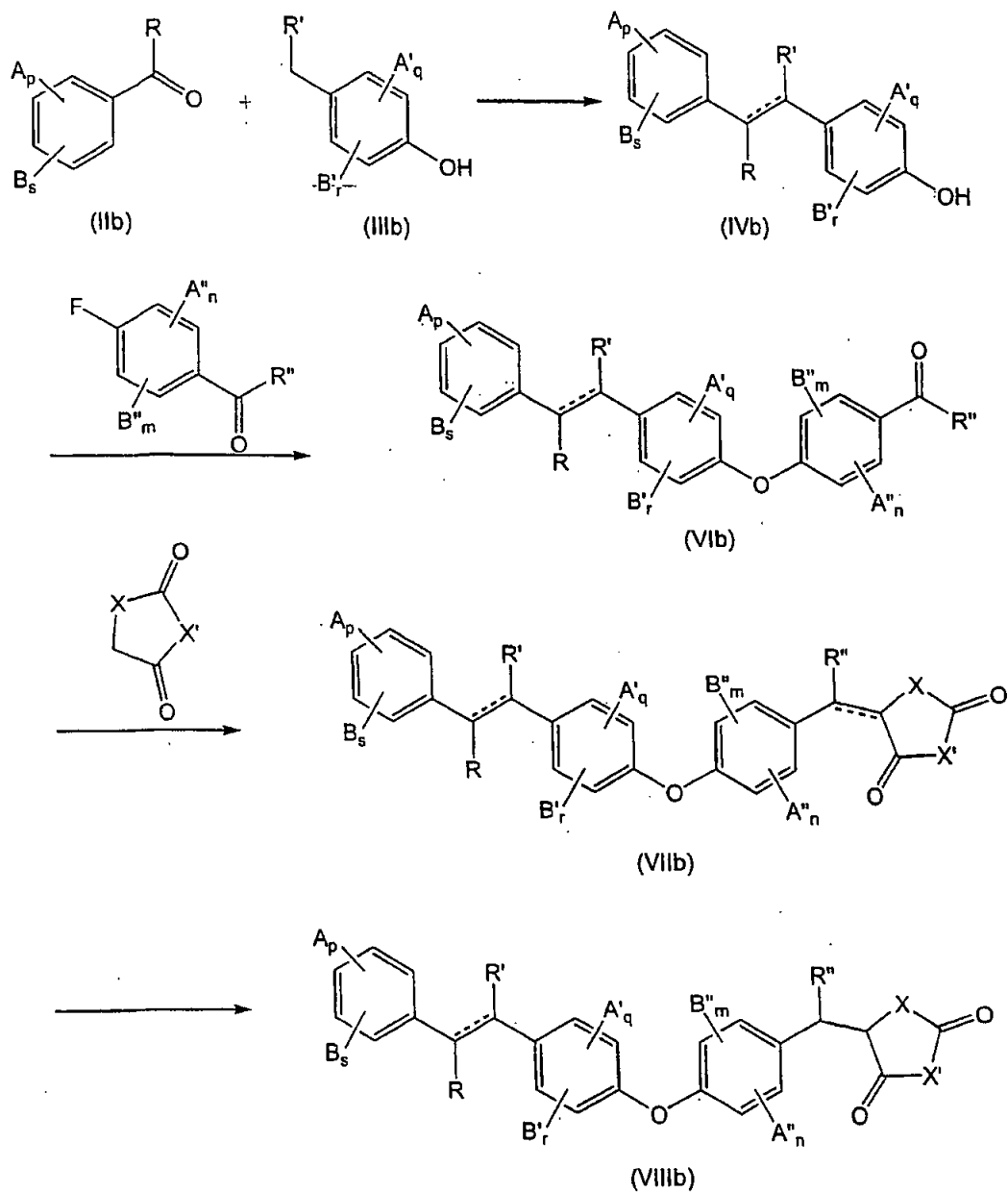
drages and suppositories, or in the liquid form, e.g., solutions, suspensions and emulsions. The preparations may also be delivered transdermally or by topical application.

- 5 Representative compounds according to the present invention may be synthesized by the methods disclosed below in Schemes IA, IB, II and III wherein Scheme IA illustrates the preparation of Compound VIII while Schemes IB, II and III describe the synthesis methods more generally.

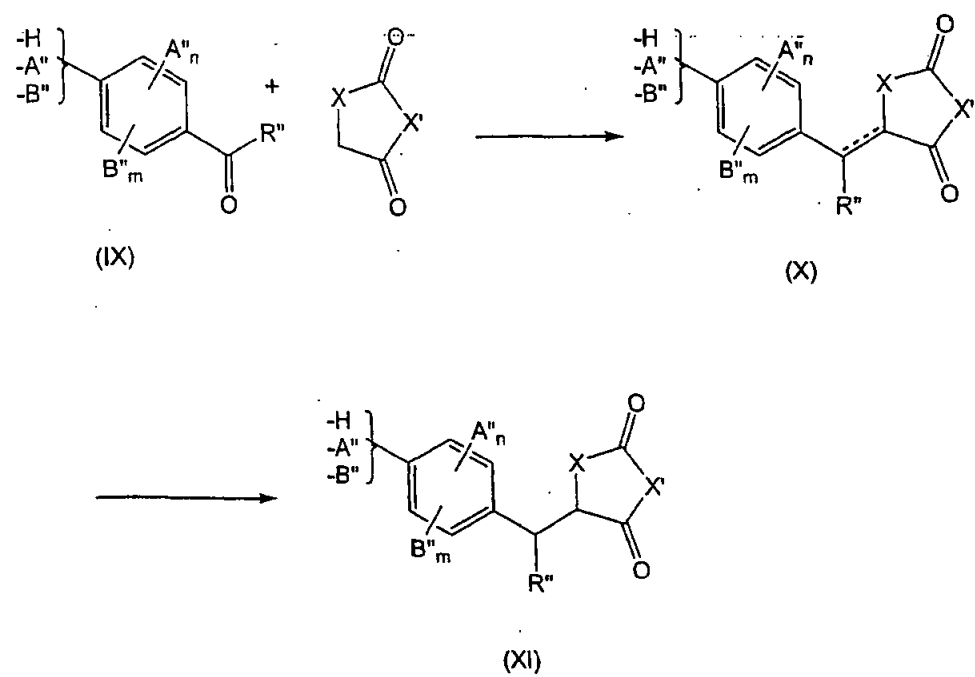
SCHEME IA



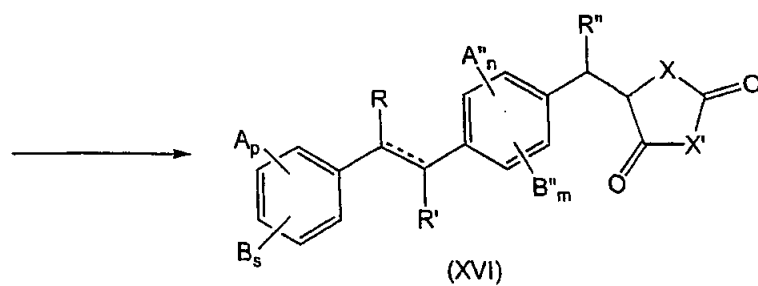
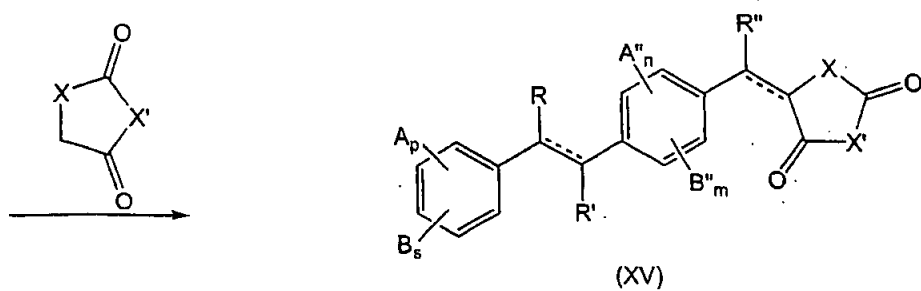
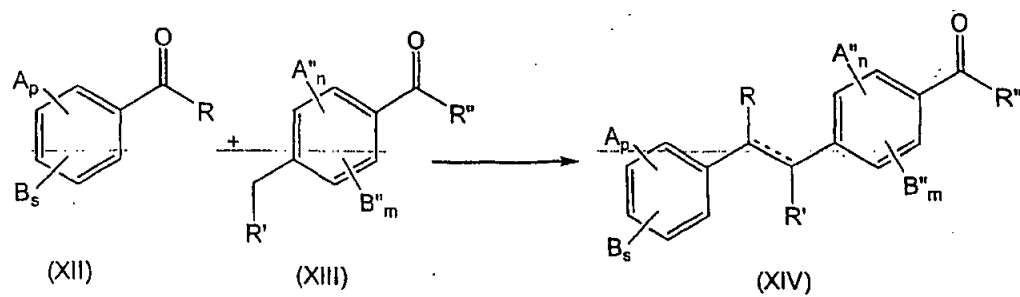
SCHEME 1B



SCHEME II



SCHEME III



Referring to Scheme IA, the aldehyde (II) and acid (III) may be condensed in acetic anhydride and triethylamine to form the unsaturated acid (IV). After esterification of the acid to provide Compound (V), the phenolic hydroxy group is formed into an ether (VI) with p-fluorobenzaldehyde. The aldehyde (VI) is then condensed with the thiazolidinedione to provide Compound (VII) and the bond exo to the heterocycle in Compound (VII) is reduced with hydrogen to form the object Compound (VIII).

The steps in Scheme IA are generalized in Scheme IB. The general formulas IIb, IIIb, IVb, VIb, VIIb and VIIIb correspond respectively to formulas II, III, IV, VI, VII and VIII in Scheme IA.

In Scheme II, the general synthesis of compounds where Z=H, A" or B" is shown. The aldehyde or ketone (IX) is condensed with the heterocyclic dione to form the bicyclic compound (X), which can be optionally hydrogenated to form the product (XI).

In Scheme III, the general synthesis of the tricyclic products (XV) and (XVI) is shown. The aldehyde or ketone (XII) is condensed with (XIII) to form the bicyclic compound (XIV). The compound (XIV) is condensed with the heterocyclic dione to form the tricyclic product (XV), which can be optionally hydrogenated to (XVI).

In Formula I, C₁-C₂₀ linear or branched alkyl means groups such as methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, t-butyl, sec-butyl, isopentyl, neopentyl, etc. The C₂-C₂₀ linear or branched alkenyl means unsaturated groups such as ethenyl, propenyl, n-butenyl, isobutenyl, including groups containing multiple sites of unsaturation such as 1,3 -butadiene, and the like. The halo groups include chloro, fluoro, bromo, iodo. Substituted C₁-C₂₀ linear or branched alkyl or substituted C₂-C₂₀ linear or branched alkenyl means that the alkyl or alkenyl groups may be substituted with groups such as halo, hydroxy, carboxyl, cyano, amino, alkoxy, and the like. The C₁-C₂₀ acylamino or acyloxy group means an oxygen or amino group bonded to an acyl group (RCO) where R can be hydrogen, C₁-C₂₀ linear or branched alkyl or C₂-C₂₀ linear or branched alkenyl. Alkenyl groups are -C=C-, where R can be

hydrogen, C₁-C₂₀ linear or branched alkyl or C₂-C₂₀ linear or branched alkyl. Alkoxycarbonyl means a group ROCO- where R can be hydrogen, C₁-C₂₀ linear or branched alkyl or C₂-C₂₀ linear or branched alkenyl. The C₁-C₂₀ alkyl carboxyl amino group means a group RCON(R)- where R can be
5 independently hydrogen, C₁-C₂₀ linear or branched alkyl or C₂-C₂₀ linear or branched alkenyl. Carboxyl is the group HO₂C-, and alkanoyl is the group RCO- wherein R is a linear or branched carbon chain. The group aroyl is Ar-CO- wherein Ar is an aromatic group such as phenyl, naphthyl, substituted phenyl, and the like. Aralkanoyl is the group Ar-R-CO- wherein Ar is a
10 aromatic group such as phenyl, naphthyl, substituted phenyl, etc. and R is a linear branched alkyl chain.

As indicated earlier, the compounds of the invention where a, b or c represents a double bond may have either the E or Z configuration. On the other hand, when a, b or c is absent, i.e. a single bond is present, the
15 resulting compounds may be R- and/or S- stereoisomers. The invention contemplates racemic mixtures of such stereoisomers as well as the individual, separated stereoisomers. The individual stereoisomers may be obtained by the use of an optically active resolving agent. Alternatively, a desired enantiomer may be obtained by stereospecific synthesis using an
20 optically pure starting material of known configuration.

The preparation of compound VIII, i.e. 5-(4-(4-(1-carbomethoxy)-2-(3,5-dimethoxy phenyl)-ethenyl)-phenoxy)-benzyl)-2,4-thiazolidinedione, is described below with reference to Scheme IA as shown earlier:

25

Example 1

(a) Synthesis of 3-(3,5-dimethoxy-phenyl)-2-(4-hydroxy-phenyl)-acrylic acid (Compound IV):

30

To a mixture of 3,5-dimethoxybenzaldehyde (500 g, 3 mol) and *p*-hydroxyphenyl acetic acid (457 g, 3 mol) was added acetic anhydride (1 L) and triethylamine (420 mL). This non-homogeneous mixture on heating

41

becomes homogeneous at ~70°C. After being stirred at 130-140 °C for 6 h, the mixture was cooled to room temperature. Concentrated HCl (1 L) was added to the reaction mixture slowly in 50 min keeping temp between 20-30 °C. The light yellow precipitate obtained was filtered and rinsed with DI water in the Buchner funnel. The solid was dissolved in 3N NaOH (5 L) and stirred for 1 h and filtered. The filtrate was acidified, maintaining a temperature at 25-30 °C, with conc. HCl to pH 1. The precipitated product was filtered and washed with water to give crude product. The crude product was recrystallized from MeOH-H₂O then dried at 40 °C for 6 h. Yield: pale yellow solid 428 g (47%). ¹HNMR(DMSO-d₆): δ 12.48(br, 1H), 9.42(s, 1H), 7.59(s, 1H), 6.95(d, J=8.0 Hz, 2H), 6.76(d, J=8.0 Hz, 2H), 6.35(t, J=2.2 Hz, 1H), 6.27(d, J=2.2 Hz, 2H), 3.56(s, 6H).

(b) Synthesis of 3-(3,5-dimethoxy-phenyl)-2-(4-hydroxy-phenyl)-acrylic acid methyl ester (Compound V):

Methanol (3L) was added to thoroughly dried Compound IV (427.5 g, 1.42 mol) under argon. To this stirred suspension concentrated sulfuric acid (100 mL) was added and heated at reflux for 20h under argon. Methanol was evaporated under reduced pressure at 30 °C. The residue was taken up in ethyl acetate (3 L) and washed with water (2x1 L), saturated aqueous Na HCO₃ (pH 8, 2x1 L), saturated aqueous sodium chloride solution (2 x 1 L). Organic layer was dried on anhydrous magnesium sulfate, filtered and the solvent was evaporated. The crude product obtained was dried thoroughly under high vacuum and used as such in the next step. Yield: white solid, 433.6g (97 %). ¹HNMR(CDCl₃): δ 7.72(s, 1H), 7.06(d, J=7.9 Hz, 2H), 6.77(d, J=7.9 Hz, 2H), 6.33(t, J=2.2 Hz, 1H), 6.26 (d, J=2.2 Hz, 2H), 5.74(s, 1H), 3.81(s, 3H), 3.60(s, 6H).

(c) Synthesis of 3-(3,5-dimethoxy-phenyl)-2-[4-(4-formyl-phenoxy)-phenyl]-acrylic acid methyl ester (Compound VI):

Under argon, Compound V (433 g, 1.37 mol) was dissolved in dry DMF
5 (1.6 L) and to this sodium hydride (60% in oil, 60.4 g, 1.51 mol) was added.
To the resulting orange solution, *p*-fluorobenzaldehyde (185 mL, 1.71 mol)
was added and heated at 80°C for 18h. The reaction mixture was cooled to
room temperature, diluted with ethyl acetate (3 L) and extracted with water (3
x 1L), then brine (1x1 L). The organic layer was dried over anhydrous sodium
10 sulfate, filtered and solvent was evaporated. The residue was suspended in
methanol (3 L) and stirred overnight. The suspension was chilled and then
filtered. Solid obtained was dried under vacuum at 40°C. Yield 445 g (77%).
¹HNMR(CDCl₃): δ 9.94 (s, 1H), 7.86 (d, J=8.6 Hz, 2H), 7.80 (s, 1H), 7.28(d,
J=8.6 Hz, 2H), 7.11(d, J=2.9 Hz, 2H), 7.08(d, J=2.9 Hz, 2H), 6.36(t, J=2.2 Hz,
15 1H), 6.25 (d, J=2.2 Hz, 2H), 3.83(s, 3H), 3.63(s, 6H).

(d) Synthesis of 3-(3,5-dimethoxy-phenyl)-2-[4-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl) -phenoxy]-phenyl]-acrylic acid methyl ester (Compound VII):

20 To a stirred suspension of Compound VI (352 g, 0.82 mol) in
anhydrous toluene (2.5 L), 2,4-thiazolidinedione (98.6 g, 0.84 mol), benzoic
acid (134 g, 1.10 mol) and piperidine (107.4 g, 1.26 mol) was added
sequentially and heated at reflux temperature with continuous removal of
water with the help of Dean-Stark apparatus for 5h. Toluene (1 L) was
25 removed from the reaction mixture and the mixture was placed overnight in a
4°C cold room. Solid separated was filtered off and mother liquor was
evaporated to dryness under reduced pressure. The residue obtained was re-
dissolved in a mixture of MeOH-diethylether (1:1, 3 L). Solution on standing
overnight at 4°C yielded more solids. The solid was filtered; both the crops
30 were pooled together and dried overnight in vacuum oven at 40°C. Yield:
362.5 g (86 %). ¹H NMR (DMSO-d₆): δ 12.53 (br, 1H), 7.78 (s, 1H), 7.73
(s, 1H), 7.63(d, J=9.2 Hz, 2H), 7.25 (d, J=9.2 Hz, 2H), 7.15 (d, J=4.3 Hz, 2H),

7.12 (d, J=4.3 Hz, 2H), 6.42 (t, J=2.2 Hz, 1H), 6.27 (d, J=2.2 Hz, 2H), 3.73 (s, 3H), and 3.59 (s, 6H).

5 (e) Synthesis of 5-(4-(4-(1-carbomethoxy)-2-(3,5-dimethoxyphenyl)-ethenyl)-phenoxy)-benzyl)-2,4-thiazolidine dione, also called 3-(3,5-dimethoxyphenyl)-2-[4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]-phenyl]-acrylic acid methyl ester (Compound VIII):

10 Compound VII (30 g, 58 mmol) was dissolved in warm dioxane (900 mL), transferred in a 2 L hydrogenation bottle and 10% Pd-C (~50 % water, 15 g) was added to this and hydrogenated in a Parr hydrogenator at 60 psi for 24 h. Following this period, an additional 15 g Pd-C was added and hydrogenation was allowed to continue for another 24 h. Catalyst was filtered
15 through a bed of Celite and solvent was evaporated.

The residue was taken up in acetonitrile (500 ml) and adsorbed on C-18 silica (50g). The adsorbed material was placed on the top of a column containing C-18 reverse phase silica gel (400 g). Column was eluted with CH₃CN in H₂O (45%, 2 L), CH₃CN in H₂O (50%, 2 L), CH₃CN in H₂O (55%, 2
20 L) to elute the undesired fractions. Fractions were collected with the start of 60% CH₃CN in H₂O elution for the desired compound. Fractions were mixed on the basis of their HPLC purity. Acetonitrile was evaporated under reduced pressure. Water was removed by lyophilization. Yield : 12g (40%). White solid; M.P. 126-128°C. ¹H NMR (DMSO-d₆) δ 12.01 (br, 1H), 7.73 (s, 1H),
25 7.28 (d, J=8.6 Hz, 2H), 7.19 (d, J=8.6 Hz, 2H), 7.02 (d, J=8.6 Hz, 2H), 6.96 (d, J=8.6 Hz, 2H), 6.40 (t, J=2.2 Hz, 1H), 6.27 (d, J=2.2 Hz, 2H), 4.92 (dd, J=9.2 and 4.4 Hz, 1H), 3.73 (s, 3H), 3.57 (s, 6H), 3.37 (dd, J=14.8 and 4.3 Hz, 1H) and 3.12 (dd, J=14.8 and 9.4 Hz, 1H); IR (KBr) ν_{max} 3200, 2950, 2850, 1700, 1600, 1500, 1350, 1150, and 850 cm⁻¹; EIMS:m/z, 518, [M-H]⁺ 265, 249,
30 and 113.

Referring to the drawings, Compound VIII was administered in a single oral dose (50mg/kg body weight) for 15 days to db/db male mice as shown in

FIG. 1A. A substantial reduction in blood glucose level was observed. There was no increase in body weight in the treatment group as compared to the control treated with the vehicle without the active ingredient, FIG. 1B.

The compound was orally administered to ob/ob mice with a single oral
5 dose (50mg/kg body weight). As shown in FIG. 2A, there was a 62% drop in blood glucose level and, similar to db/db mice, there was no significant increase in body weight between the control and the treatment groups as shown in FIG. 2B. This is in contrast to treatment of diabetic animals by thiazolidinedione type compounds which are known to be associated with
10 increase in body weight. See Okuno et al., *J. Clin. Invest.*, 101, 1354-1361 (1998) and Yoshioka et al., *Metabolism*, 42, 75-80 (1993). By stopping treatment after day 15 in both models, there was shown an increase in glucose level as depicted in FIGS. 3A and 3B. The time course of the drug effect is shown in FIG. 4. Oral administration of a single dose of the
15 compound in db/db mice was effective for 24 hours and beyond.

The triglyceride levels were also measured. Triglycerides, which are esters of fatty acids and glycerol, do not freely circulate in plasma but are bound to proteins and transported as macromolecular complexes called lipoproteins. The triglycerides were measured by the enzymatic method
20 described by McGowen et al., 1983, with a modification to determine the triglyceride levels in db/db and ob/ob mice. There was shown a 24% drop in triglyceride levels in db/db mice (FIG. 5A) after 15 days of treatment with the compound and in ob/ob mice, a 65% decrease in triglyceride as compared to the control (FIG. 6B) after treatment for 10 days.

The free fatty acids (FFA) were enzymatically measured using coenzyme A in the presence of acyl CoA synthase (Wako Chemicals USA). The free fatty acid levels in db/db and ob/ob mice treated with the compound were significantly lower compared to the control animals. A 34% drop in FFA levels in db/db mice (FIG. 5B) was shown after 15 days of treatment with the
30 compound. In ob/ob mice, after 10 days of treatment, a lowering of 33% of FFA was shown compared to the control (FIG. 6C).

The percentage of glycohemoglobin (GHb) in blood reflects the average blood glucose concentration. It is a measure of overall diabetic control and can be used to monitor the average blood glucose levels. The glycosylation of hemoglobin occurs continuously in the red blood cells. But
5 since the reaction is non-enzymatic and irreversible, the concentration of glycohemoglobin in a cell reflects the average blood glucose levels seen by the cell during its life. An assay was conducted using affinity chromatography with boronate as described by Abraham et al., *J. Lab. Clin. Med.*, 102, 187 (1983). There is a 0.7% drop in the GHb level in db/db mice (FIG. 5C) after
10 15 days of treatment with the compound and in ob/ob mice after 14 days of treatment, there is 1.3% decrease (FIG. 6D) in the GHb level compared to the control.

The blood insulin level was measured by ELISA following a standard protocol. A 58% drop of serum insulin in ob/ob mice (FIG. 6A) was shown
15 after 10 days of treatment with the compound, thus, demonstrating its ability to act as an insulin sensitizer.

Obesity is considered a significant risk factor for various adult diseases such as diabetes and cardiac disease. Leptin, an obese gene product, has been identified from the investigation of ob/ob mice, where the leptin is lacking
20 because of a mutation in that gene (Zhang et al., *Nature*, 372, 425 (1994). Leptin is a protein of about 16kDa, which is expressed in adipose tissue, and which promotes weight loss by suppressing appetite and stimulating metabolism. It is currently believed that leptin plays a key role in the obesity syndrome. In the db/db mice according to the experiment, the leptin level was
25 measured by an ELISA, following a standard protocol. After 15 days of treatment with the compound, there is a 23% increase (FIG. 5D) in the serum leptin level compared to the control group.

The liver enzymes glutamic oxalacetic transaminase/aspartate aminotransferase (AST/GOT) and glutamic pyruvic transaminase/alanine
30 aminotransferase (ALT/GPT) were assayed in the sera of ob/ob mice after 21 days of treatment (orally, 50 mg/kg) of the test compound. The test was also

conducted using troglitazone. These enzyme levels are found to elevate in several kinds of hepatic disorders or liver necrosis. In FIG. 7A, the AST level in the mice was not elevated compared to untreated mice or to mice treated with troglitazone. Similarly, FIG. 7B shows that the ALT level did not elevate
5 compared to untreated mice or mice treated with troglitazone.

Referring to FIG. 8 glucose uptake in 3T3-L1 differentiated adipocytes was measured after treatment with the test compound. The assay was conducted according to the method of Tafuri, *Endocrinology*, 137, 4706-4712 (1996). The serum-starved cells were treated with the test compound for 48
10 hours at different concentrations, then washed and incubated in glucose-free media for 30 minutes at 37°C. Then ¹⁴C- deoxyglucose was added and uptake was monitored for 30 minutes under incubation. After washing, the cells were lysed (0.1% SDS) and counted. As shown in FIG. 8, there is a 3.5 to 4-fold increase in glucose uptake at the indicated concentrations of the test
15 compound with respect to basal levels.

Referring to FIG. 9, RAW cells were preincubated with either Compound VIII or rosiglitazone (0.1, 1, 10, 50 or 100 µM) for 1 hour at 37°C in RPMI-1640 containing 10% FBS. After 1 hour, LPS (0.1 µg/ml) was added and cells were incubated an additional 6 hours. Cell supernatant was then
20 collected, aliquoted and frozen at -70°C, and an aliquot used to determine TNF-alpha concentration by ELISA. Compound VIII was a better inhibitor of TNF-alpha than rosiglitazone.

Referring to FIG. 10, RAW cells were preincubated with either Compound VIII or rosiglitazone (0.1, 1, 10, 50 or 100 µM) for 1 hour at 37°C in
25 RPMI-1640 containing 10% FBS. After 1 hour LPS (0.1 µg/ml) was added and cells were incubated an additional 6 hours. Cell supernatant was then collected, aliquoted and frozen at -70°C, and an aliquot used to determine the concentration of IL-6 by ELISA. Compound VIII was a better inhibitor of IL-6 than rosiglitazone.

30 Referring to FIG. 11, RAW cells were preincubated with either Compound VIII or rosiglitazone (0.1, 1, 10, 50 or 100 µM) for 1 hour at 37°C in

RPMI-1640 containing 10% FBS. After 1 hour LPS (0.1 µg/ml) was added and cells were incubated an additional 6 hours. Cell supernatant was then collected, aliquoted and frozen at -70°C, and an aliquot used to determine the concentration of IL-1-beta by ELISA. Compound VIII inhibited IL-1-beta better
5 than rosiglitazone.

Referring to FIGS 12A AND 12B, RAW cells were preincubated with either Compound VIII (12A) or rosiglitazone (12B) (0.1, 1, 10, 50 or 100 µM) for 1 hour at 37°C in RPMI-1640 containing 10% FBS. After 1 hour LPS (0.1 µg/ml) was added and cells were incubated an additional 6 hours. Cell
10 supernatant was then collected, aliquoted and frozen at -70°C, and aliquots used to determine COX-2 and COX-1 activity. Compound VIII, but not rosiglitazone, inhibited the activity of COX-2 (as measured by PGE2 production in a 50 µl sample). Neither compound inhibited COX-1 activity.

The transcription factor NF-kappaB coordinates the activation of many
15 genes involved in the response to pro-inflammatory cytokines, and, therefore, plays a key role in the development of inflammatory diseases. NF-kappaB is activated by phosphorylation of the inhibitory protein IkappaB. To examine the effect of compound VIII on the LPS-stimulated phosphorylation of IkappaB, RAW 264.7 cells were preincubated with vehicle only, 15-deoxy-
20 $\Delta^{12,14}$ -prostaglandin J₂ (3 µM) as a positive control, compound VIII (3, 10 or 30 µM), or rosiglitazone (3, 10 or 30 µM) for 1 hr. at 37°C. Then, cells were treated with or without LPS (10 ng/ml) plus IFN-gamma (10 U/ml) for 5 min. or 15 min. at 37°C. Cells were then lysed, and the cell lysates (27 µg/lane) were separated by electrophoresis on a 4-20% polyacrylamide gel, blotted onto a
25 nitrocellulose membrane and probed with anti-phospho-IkappaB antibody. The results revealed that compound VIII, but not rosiglitazone, exhibited dose-dependent inhibition of the phosphorylation of IkappaB.

Figures 13A-D illustrate the suppression of collagen-induced arthritis by treatment with Compound VIII. Arthritis was induced by intradermal
30 administration of collagen (100 µg/mouse) in complete adjuvant in make DBA/1Lac mice of 7 weeks. The booster (100 µg/mouse) immunization in

incomplete adjuvant was given subcutaneously on Day-21. Two days later when arthritic scores were around 1, the animals were divided into two groups. One group received 50 mg/kg dose of Compound VIII orally for 17 days daily. The second group received 10% PEG in water and was used as a vehicle treated group. Body weight (Figure 13A), Clinical score (Figure 13B), Joints affected (Figure 13C) and Paw thickness (Figure 13D) were monitored 24 hours after the drug administration at different time intervals. As shown in the Figures, the mice treated with Compound VIII showed significantly lower clinical scores, joints affected and paw thickness when compared to the vehicle treated group. There was no change in body weight between the vehicle and the treatment groups.

Experimental allergic encephalomyelitis (EAE) is an autoimmune demyelinating inflammatory disease of the central nervous system. EAE exhibits many of the clinical and pathological manifestations of human multiple sclerosis (MS), and it serves as an animal model to test potential therapeutic agents for MS (Scolding et al, Prog. Neurobiol., 43:143-73, 2000). Figure 14 illustrates the suppression of EAE by Compound VIII. Active EAE was induced in SJL/J mice essentially according to the method of Owens and Sriram (Neurol Clin, 13:51-73, 1995). Naïve mice were immunized subcutaneously with 400 µg each of mouse spinal cord homogenate in complete Freund's adjuvant on day 0 and day 7. Mice were then treated once daily by subcutaneous injection with 50 µg or 200 µg of Compound VIII or with vehicle only. Paralysis was graded according to the numeric scale indicated. As evidenced by the dramatic reduction in clinical score shown in Figure 14, treatment with the 200 µg dose of Compound VIII was highly effective in ameliorating EAE.

It will be evident from the above that the compounds according to the present invention, as represented by Compound VIII, not only lower blood glucose level, triglyceride level, free fatty acid level, glycohemoglobin and serum insulin, but also raise the leptin level while showing no significant increase in body weight or liver toxicity. The compounds also inhibit TNF-

alpha, IL-6, IL-1 β production and COX-2 activity in vitro and, as shown by Figures 13A-13D and 14, the compounds can be used to suppress arthritis and potentially to treat multiple sclerosis, respectively. The properties demonstrated above indicate that the compounds of the invention should be
5 useful in the treatment of disorders associated with insulin resistance, hyperlipidemia, coronary artery disease and peripheral vascular disease and for the treatment of inflammation, inflammatory diseases, immunological diseases and cancer, especially those mediated by cytokines and cyclooxygenase.

10 While the invention has been exemplified above by reference to the preparation and use of compound VIII, it will be understood that the invention is of broader application consistent with the scope of compounds represented by Formula I. This includes, for example, compound VII, which is not only useful as an intermediate for preparing compound VIII as shown but also
15 demonstrates useful biological activity of its own consistent with the activities of compound VIII.

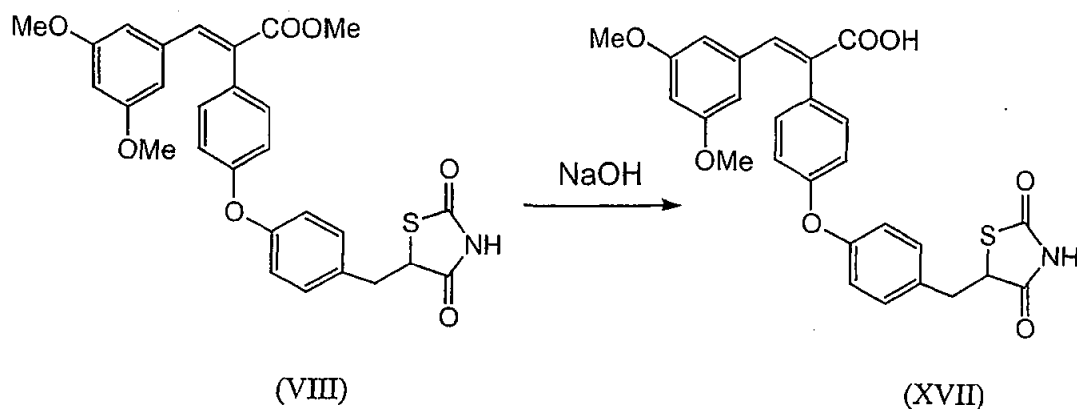
The synthesis of other compounds representative of the scope of the invention is illustrated by the examples which follow:

20 Example 2

Synthesis of 3-(3,5-dimethoxyphenyl)-2-[4-[4-(2,4-dioxothiazolidin-5-ylmethyl)-phenoxy]-phenyl]-acrylic acid (Compound XVII)

Compound XVII a metabolite of compound VIII, may be prepared by hydrolysis of compound VIII according to the following reaction scheme:

25



5

To a stirred, cooled below 10°C, suspension of 3-(3,5-dimethoxyphenyl)-2-{4-[4-(2,4-dioxothiazolidin-5-ylmethyl)-phenoxy]-phenyl}-acrylic acid methyl ester (compound VIII) in methanol (50mL), aqueous sodium hydroxide (2N, 50 mL) was added and stirred for 15h at room temperature. The resulting pale yellow solution was cooled to 10°C and acidified with aqueous HCl (5%, 115 mL). The solid separated was filtered and washed with water (3 x 30 mL), recrystallized from methanol and dried to give a product characterized as follows:

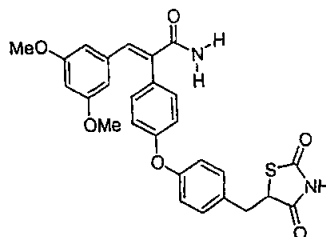
¹H NMR (DMSO-d₆) δ 7.69(s, 1H), 7.28 (d, J=8.8 Hz, 2H), 7.19 (d, J=8.8 Hz, 2H), 7.02 (d, J=8.8 Hz, 2H), 6.97 (d, J=8.8 Hz, 2H), 6.41 (t, J=2.4 Hz, 1H), 6.28 (d, J=2.4 Hz, 2H), 4.92 (dd, J=9.2 and 4.4 Hz, 1H), 3.58 (s, 6H), 3.38 (dd, J=14.0 and 4.0 Hz, 1H) and 3.13 (dd, J=14.4 and 9.2 Hz, 1H).

Example 3

20 Synthesis of 3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-acrylamide (Compound XVIII)

Compound XVIII, which may be represented by the formula:

25



was prepared as follows from compound (XVII):

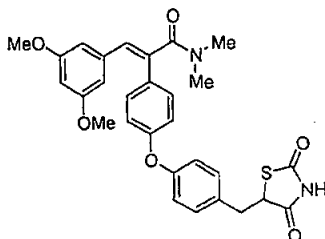
- 5 A clean dry flask with stirbar was charged with compound (XVII) (0.423g, 0.837 mmol) and dry DMF (10 mL). Then with stirring carbonyldiimidazole (0.271g, 1.67 mmol) was added and the reaction was heated to 60°C for 1h while vented through an oil bubbler. The reaction mixture was then cooled to 0°C and 2M ammonia in methanol (2.1 mL, 4.2 mmol) was added. The
- 10 reaction was worked up by partitioning the mixture with 10% citric acid (10mL), ethyl acetate (50mL), and water (40mL). The organic phase was then rinsed sequentially with water (2 X 30mL), brine (1 X 20mL) and dried with anhydrous magnesium sulfate. Concentration of the organics afforded crude product. The crude product was purified by silica gel chromatography
- 15 using ethyl acetate-hexanes (1:1) in 1% acetic acid to ethyl acetate-hexanes (3:2) in 1% acetic acid gradient elution. Concentration of the appropriate fractions yielded 200mg (47%) of the white-light yellow primary amide as a solid. Analysis: ¹H-NMR, 400MHz (DMSO-d₆): δ12.06 (br, 1H), 7.40 (s, 1H), 7.34 (br, 1H), 7.27 (d, J=8.4 Hz, 2H), 7.18 (d, J=8.8 Hz, 2H), 7.05 (d, J=9.2
- 20 Hz, 2H), 6.98(d, J=8.4 Hz, 2H), 6.93 (br, 1H), 6.36(m, 1H), 6.20 (s, 1H), 6.19 (s, 1H), 4.91(dd, J=4.0Hz, 1H), 3.57 (s, 6H), 3.12 (dd, J=9.2Hz, 1H).

Example 4

- 25 Synthesis of 3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-N,N-dimethyl-acrylamide (Compound XIX):

Compound (XIX) represented by the formula:

30



was prepared as follows:

A clean dry flask with stirbar was charged with compound (XVII) (0.422g, 0.835 mmol) and dry DMF (10 mL). Then with stirring carbonyldiimidazole (0.271g, 1.67 mmol) was added and the reaction was heated to 60°C for 1h while vented through an oil bubbler. The reaction mixture was then cooled to 0°C and a 2M dimethylamine in THF (2.1mL, 4.2 mmol) solution was added. The reaction was worked up by partitioning the mixture with 10% citric acid (10mL), ethyl acetate (50mL), water (40mL). The organic phase was then rinsed sequentially with water (2 X 30mL), brine (1 X 20mL) and dried with anhydrous magnesium sulfate. Concentration of the organics afforded crude product. The crude product was purified by silica gel chromatography using ethyl acetate-hexanes (3:2) in 1% acetic acid elution. Concentration of the fractions yielded 381mg (86%) of the off-white tertiary dimethylamide as a solid. Analysis: ¹H-NMR, 400MHz (DMSO-d₆): δ11.97 (br, 1H), 7.29 (d, J=8.8 Hz, 2H), 7.27 (d, J=8 Hz, 2H), 6.99 (d, J=8.8 Hz), 6.95(d, J=8.8 Hz, 2H), 6.57 (s, 1H), 6.35 (m, 1H), 6.29 (s, 1H), 6.28 (s, 1H), 4.91(dd, J=4.4 Hz, 1H), 3.58 (s, 6H), 3.12 (dd, J=9.2Hz, 1H), 3.05 (br, 3H), 2.91 (s, 3H).

Example 5

Synthesis of, 3-(3,5-dimethoxy-phenyl)-2-[4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl]-N-methoxy,-N-methyl-acrylamide (Compound XX):

Compound (XX) was prepared as follows:

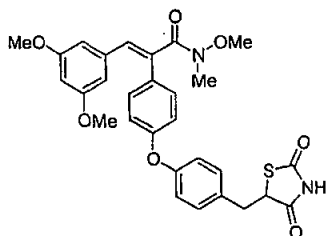
A clean dry flask with stirbar was charged with compound (XVII) (0.450g, 0.890 mmol) and dry DMF (10 mL). Then, with stirring, carbonyldiimidazole (0.29g, 1.78 mmol) was added and the reaction was heated to 60°C for 1h while vented through an oil bubbler. The reaction mixture was then cooled to 0°C and *N*-methyl-*N*-methoxyhydroxylamine hydrochloride (0.434g, 4.45 mmol) in water (10 mL) and triethylamine (0.62

mL) was added and stirred overnight. The reaction was worked up by partitioning the mixture with 10% citric acid (10mL), ethyl acetate (50mL), and water (40mL). The organic phase was then rinsed sequentially with water (2 X 30mL), brine (1 X 20mL) and dried with anhydrous magnesium sulfate.

- 5 Concentration of the organics afforded crude product. The crude product was purified by silica gel chromatography using ethyl acetate-chloroform (1:5) elution. Concentration of the appropriate fractions yielded 400mg (82%) of the off-white tertiary *N*-methyl-*N*-methoxyamide as a solid. Analysis: ¹H-NMR, 400MHz (DMSO-d₆): δ12.06 (br, 1H), 7.27 (d, J= 9.2 Hz, 2H), 7.26 (d, J=8.8 Hz, 2H), 7.00 (d, J=8.8 Hz), 6.95 (d, J=8.4 Hz, 2H), 6.57 (s, 1H), 6.35 (m, 1H), 6.29 (s, 1H), 6.28 (s, 1H), 4.91(dd, J=4.4 Hz, 1H), 3.58 (s, 6H), 3.12 (dd, J=9.2 Hz, 1H), 3.05 (br, 3H), 2.91 (s, 3H).

Compound (XX) may be structurally shown as follows:

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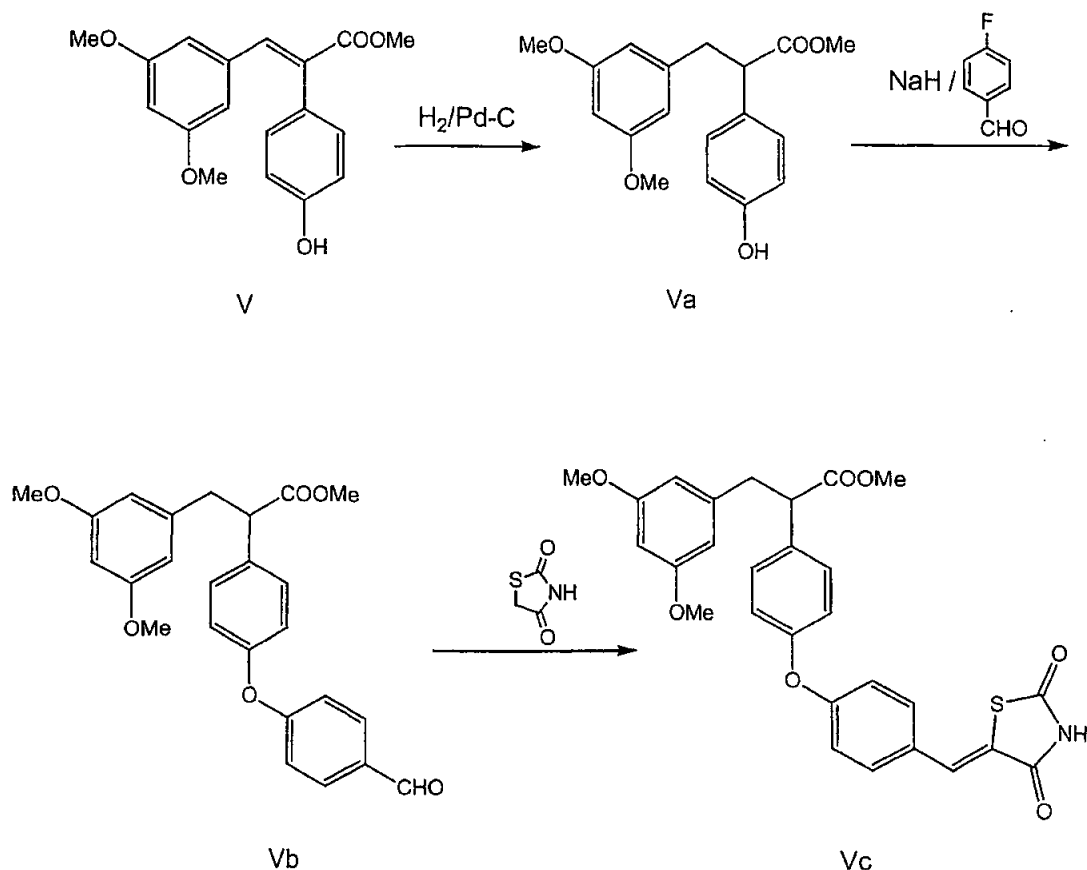


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Example 6

25 Synthesis of 3-(3,5-Dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-phenyl}-propionic acid methyl ester, (Compound Vc)

Compound Vc was prepared according to the following reaction scheme:



- 5 (a) Synthesis of 3-(3,5-Dimethoxy-phenyl)-2-(4-hydroxy-phenyl)-propionic acid methyl ester, (Compound Va):

To a suspension of 3-(3,5-dimethoxy-phenyl)-2-(4-hydroxy-phenyl)-acrylic acid methyl ester (2.1g) in dioxane (60 mL) 10% palladium on carbon
 10 (50% wet, 2.1g) was added. Hydrogenation was carried out in a Parr shaker at 70 psi for 6.5h. Catalyst was filtered through a bed of Celite and solvent was evaporated. Yield: quantitative. Analysis: ^1H NMR ($CDCl_3$): δ 7.15(d, $J=8.7$ Hz, 2H), 6.74 (d, $J=8.7$ Hz, 2H), 6.29(t, $J=2.4$ Hz, 1H), 6.25(d, $J=2.4$ Hz, 2H), 3.78(t, $J=8.7$ Hz, 1H), 3.72(s, 6H), 3.62(s, 3H), 3.31(dd, $J=13.5$ & 8.4 Hz,
 15 1H), 2.93(dd, $J=13.5$ & 6.9 Hz, 1H).

- (b) Synthesis of 3-(3,5-Dimethoxy-phenyl)-2-[4-(4-formyl-phenoxy)-phenyl]-propionic acid methyl ester, (Compound Vb):

To a suspension of sodium hydride (60% in oil, 0.25g, 6.3mmol) in DMF (2 mL) under argon, **Va** (2.0 g, 6.3mmol) in dry DMF (3mL) was added. To the resulting yellow solution, *p*-fluorobenzaldehyde (0.68mL, 6.3mmol) was added and heated at 80°C for 18h. The reaction mixture was cooled to room temperature, water (20mL) was added and extracted with ethyl acetate (3x 50 mL). The organic layer was dried over sodium sulfate, filtered and solvent was evaporated. The crude product was filtered through a small bed of silica gel. Yield: 1.83g(68.8%). Analysis: ¹HNMR(DMSO-d₆): δ9.91 (s, 1H), 7.84 (d, J=8.7 Hz, 2H), 7.33(d, J=8.7 Hz, 2H), 7.04(d, J=5.4Hz, 2H), 7.01(d, J=5.4 Hz, 2H), 6.30(t, J=2.1 Hz, 1H), 6.25 (d, J=2.1 Hz, 2H), 3.86(t, J=7.8Hz, 1H), 3.76(s, 6H), 3.66(s, 3H), 3.36(dd, J=12.6 and 8.1 Hz, 1H), 2.97(dd, J=13.5 & 7.5 Hz, 1H).

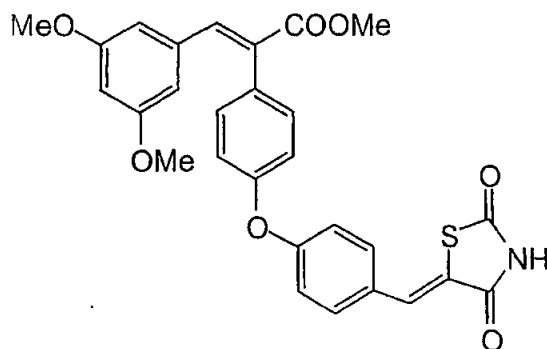
- 15 (c) Synthesis of 3-(3,5-Dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-phenyl}-propionic acid methyl ester, (Compound Vc):

To a stirred suspension of **Vb** (1.81 g, 4.3mmol) in anhydrous toluene (25 mL), 2,4-thiazolidinedione (0.56 g, 4.74mmol); benzoic acid (0.68 g, 5.60mmol) and piperidine (0.60mL, 6.03mmol) was added sequentially and heated at reflux temperature with continuous removal of water with the help of Dean-Stark apparatus for 2h. Solvent was evaporated to dryness under reduced pressure. The residue obtained was purified by silica gel chromatography, eluted with hexane-ethyl acetate (1:1) to yield **Vc**. Yield: 1.82g (81.3 %) Analysis: ¹H NMR (DMSO-d₆): δ12.53 (br, 1H), 7.76 (s, 1H), 7.60(d, J=8.7 Hz, 2H), 7.35 (d, J=8.7 Hz, 2H), 7.07 (d, J=4.8 Hz, 2H), 7.03 (d, J=4.8 Hz, 2H), 6.33-6.28 (m, 3H), 4.01(t, J=7.5Hz, 1H), 3.66(s, 6H), 3.56(s, 3H), 3.22(dd, J=13.8 & 8.4 Hz, 1H), 2.90(dd, J=13.5 & 7.2 Hz, 1H).

Other specific compounds representative of the invention include the following:

(a) 3-(3,5-dimethoxy-phenyl)-2-(4-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-phenyl)-acrylic acid methyl ester

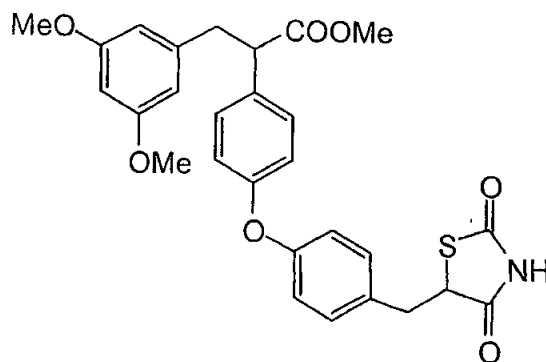
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(b) 3-(3,5-dimethoxy-phenyl)-2-(4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl)-propionic acid methyl ester

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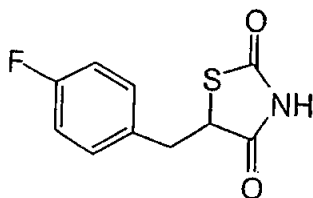
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The following additional compounds may also be mentioned as examples of compounds within the broader scope of the invention:

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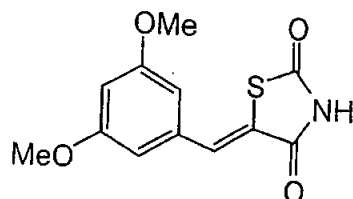
5-(4-fluoro-benzyl)-thiazolidine-2,4-dione

30



5-(3,5-dimethoxy-benzylidene)-thiazolidine-2,4-dione

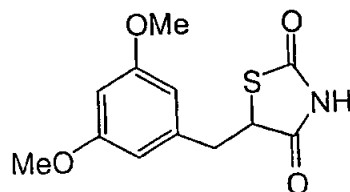
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5-(3,5-dimethoxy-benzyl)-thiazolidine-2,4-dione

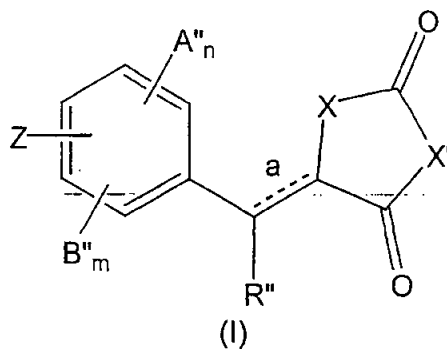
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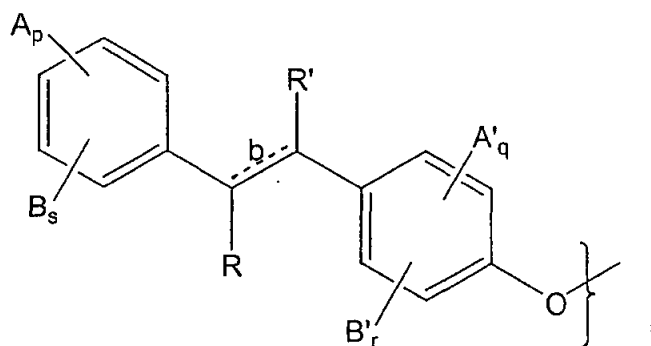
It will be appreciated that various modifications may be made in the invention as described above and as defined in the following claims wherein:

What is claimed is:

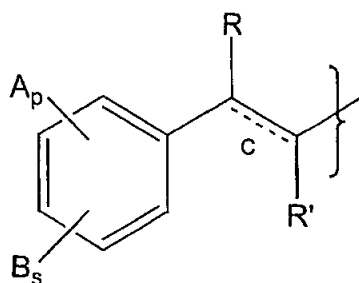
1. A compound of a formula I:



wherein Z is



H; A''; B''; or



- 5 n, m, q and r are independently integers from zero to 4 provided that $n + m \leq 4$ and $q + r \leq 4$; p and s are independently integers from zero to 5 provided that $p + s \leq 5$; a, b and c are double bonds which may be present or absent;

when present; the double bonds may be in the E or Z configuration and, when absent, the resulting stereocenters may have the R- or S- configuration;

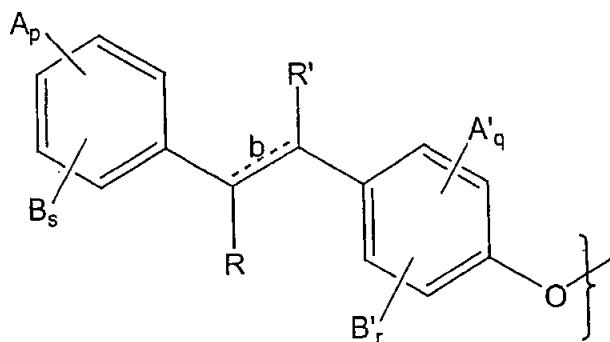
5 R, R' and R'' are independently H, C₁-C₂₀ linear or branched alkyl, C₂-C₂₀ linear or branched alkenyl, -CO₂Z', wherein Z' is H, sodium, potassium, or other pharmaceutically acceptable counter-ion such as calcium, magnesium, ammonium, tromethamine, and the like; -CO₂R''', -NH₂, -NHR''', -NR₂'', -OH, -OR''', halo, substituted C₁-C₂₀ linear or branched alkyl or substituted C₂-C₂₀ linear or branched alkenyl, wherein R''' is C₁-C₂₀ linear or branched alkyl or
10 linear or branched alkenyl;

A, A' and A'' are independently H, C₁-C₂₀ acylamino;
C₁-C₂₀ acyloxy; C₁-C₂₀ alkanoyl;
C₁-C₂₀ alkoxycarbonyl; C₁-C₂₀ alkoxy;
15 C₁-C₂₀ alkylamino; C₁-C₂₀ alkylcarboxylamino; carboxyl; cyano;
halo; hydroxy;

B, B' and B'' are independently H;
C₁-C₂₀ acylamino; C₁-C₂₀ acyloxy; C₁-C₂₀ alkanoyl;
20 C₁-C₂₀ alkenoyl; C₁-C₂₀ alkoxycarbonyl;
C₁-C₂₀ alkoxy; C₁-C₂₀ alkylamino;
C₁-C₂₀ alkylcarboxylamino; aroyl, aralkanoyl; carboxyl; cyano; halo;
hydroxy;

or A and B together, or A' and B' together, or A'' and B'' together, may be
25 joined to form a methylenedioxy or ethylenedioxy group; and
X, X' are independently -NH, -NR''', O or S.

2. A compound according to claim 1, wherein Z is

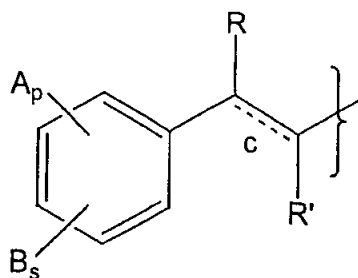


3. A compound according to claim 1, wherein Z is hydrogen.

5 4. A compound according to claim 1, wherein Z is A''.

5. A compound according to claim 1, wherein Z is B''.

10 6. A compound according to claim 1, wherein Z is



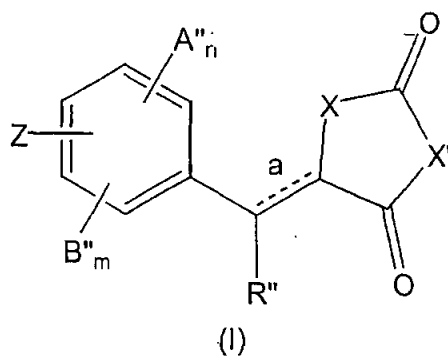
7. A compound according to claim 2, wherein X is sulfur, X' is -NH;
A''_n, B'', B', A_p, A'_q, R and R'' are all hydrogen.

15

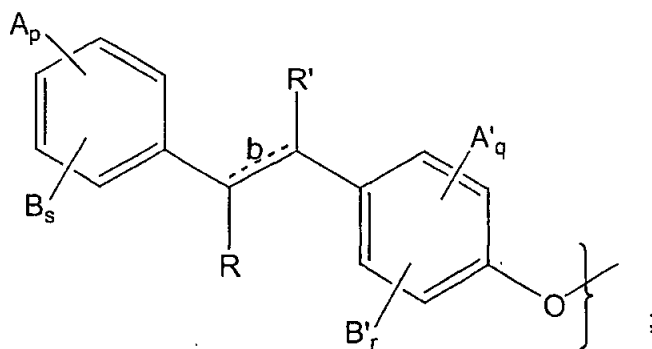
8. A compound according to claim 7, wherein B is methoxy, s is 2 and
R' is carbomethoxy.

9. A compound according to claim 8, which is 5-(4-(1-carbomethoxy-2-(3,5-dimethoxy phenyl) ethenyl)-phenoxy)-benzyl)-2,4-thiazolidinedione.

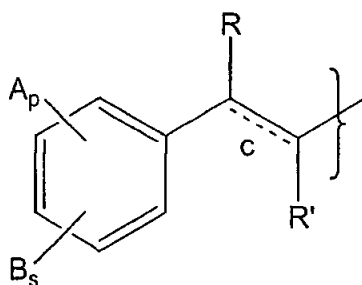
5 10. A pharmaceutical composition comprising a therapeutically effective amount of a compound of the formula I:



wherein Z is



H; A''; B''; or



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n, m, q and r are independently integers from zero to 4 provided that $n + m \leq 4$ and $q + r \leq 4$; p and s are independently integers from zero to 5 provided that $p + s \leq 5$; a, b and c are double bonds which may be present or absent; when present, the double bonds may be in the E or Z configuration and, when

5 absent, the resulting stereocenters may have the R- or S- configuration;

R, R' and R'' are independently H, C₁-C₂₀ linear or branched alkyl, C₂-C₂₀ linear or branched alkenyl, -CO₂Z', where Z' is H, sodium, potassium, or other pharmaceutically acceptable counter-ion such as calcium, magnesium,

10 ammonium, tromethamine, and the like; -CO₂R''', -NH₂, -NHR''', -NR₂'', -OH, -OR''', halo, substituted C₁-C₂₀ linear or branched alkyl or substituted C₂-C₂₀ linear or branched alkenyl, wherein R''' is C₁-C₂₀ linear or branched alkyl or linear or branched alkenyl;

15 A, A' and A'' are independently H, C₁-C₂₀ acylamino;

C₁-C₂₀ acyloxy; C₁-C₂₀ alkanoyl;

C₁-C₂₀ alkoxycarbonyl; C₁-C₂₀ alkoxy;

C₁-C₂₀ alkylamino; C₁-C₂₀ alkylcarboxylamino; carboxyl; cyano;

halo; hydroxy;

20

B, B' and B'' are independently H;

C₁-C₂₀ acylamino; C₁-C₂₀ acyloxy; C₁-C₂₀ alkanoyl;

C₁-C₂₀ alkenoyl; C₁-C₂₀ alkoxycarbonyl;

C₁-C₂₀ alkoxy; C₁-C₂₀ alkylamino;

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C₁-C₂₀ alkylcarboxylamino; aroyl, aralkanoyl; carboxyl; cyano; halo;

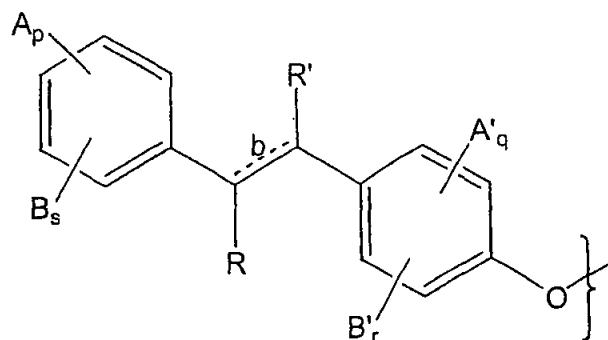
hydroxy;

or A and B together, or A' and B' together, or A'' and B'' together, may be joined to form a methylenedioxy or ethylenedioxy group; and

X, X' are independently -NH, -NR''', O or S.

30 in a physiologically acceptable carrier.

11. A composition according to claim 10, wherein Z is



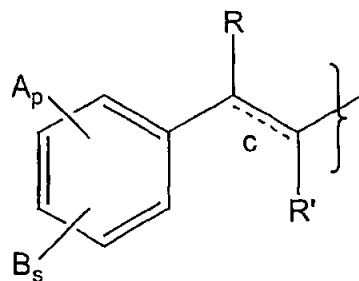
5

12. A composition according to claim 10, wherein Z is A''.

13. A composition according to claim 10, wherein Z is B''.

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14. A composition according to claim 10, wherein Z is



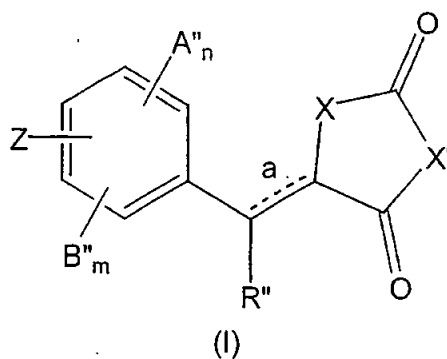
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15. A composition according to claim 10, wherein X is sulfur, X' is -NH and A'', B'', A'_q, B', A_p, R and R'' are all hydrogen.

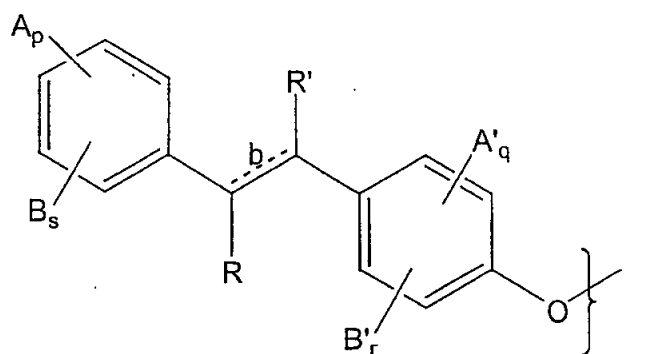
16. A composition according to claim 15, wherein R' is carbomethoxy; B is methoxy and s is 2.

17. A composition according to claim 16, wherein said compound is 5-(4-(4-(1-carbomethoxy-2-(3,5 dimethoxy phenyl) ethenyl) -phenoxy)-benzyl)-2,4-thiazolidinedione.

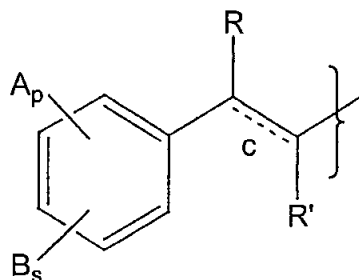
5 18. A method of treating diabetes comprising the steps of administering to a subject suffering from a diabetic condition, a therapeutically effective amount of a compound according to the formula I:



wherein Z is



H; A''; B''; or

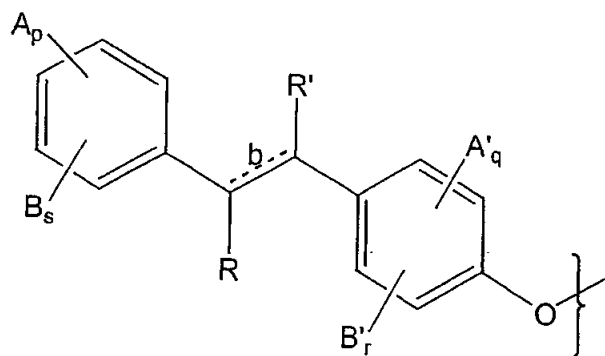


- n, m, q and r are independently integers from zero to 4 provided that $n + m \leq 4$ and $q + r \leq 4$; p and s are independently integers from zero to 5 provided that $p + s \leq 5$; a, b and c are double bonds which may be present or absent; when present, the double bonds may be in the E or Z configuration and, when absent, the resulting stereocenters may have the R- or S- configuration;
- 10 R, R' and R'' are independently H, C₁-C₂₀ linear or branched alkyl, C₂-C₂₀ linear or branched alkenyl, -CO₂Z', where Z' is H, sodium, potassium, or other pharmaceutically acceptable counter-ion such as calcium, magnesium, ammonium, tromethamine, and the like; -CO₂R''', -NH₂, -NHR''', -NR₂'', -OH, -OR''', halo, substituted C₁-C₂₀ linear or branched alkyl or substituted C₂-C₂₀
- 15 linear or branched alkenyl, wherein R''' is C₁-C₂₀ linear or branched alkyl or linear or branched alkenyl;
- A, A' and A'' are independently H, C₁-C₂₀ acylamino;
C₁-C₂₀ acyloxy; C₁-C₂₀ alkanoyl;
20 C₁-C₂₀ alkoxycarbonyl; C₁-C₂₀ alkoxy;
C₁-C₂₀ alkylamino; C₁-C₂₀ alkylcarboxylamino; carboxyl; cyano;
halo; hydroxy;
- B, B' and B'' are independently H;
25 C₁-C₂₀ acylamino; C₁-C₂₀ acyloxy; C₁-C₂₀ alkanoyl;
C₁-C₂₀ alkenoyl; C₁-C₂₀ alkoxycarbonyl;
C₁-C₂₀ alkoxy; C₁-C₂₀ alkylamino;
C₁-C₂₀ alkylcarboxylamino; aroyl, aralkanoyl; carboxyl; cyano; halo;
hydroxy;

or A and B together, or A' and B' together, or A'' and B'' together, may be joined to form a methylenedioxy or ethylenedioxy group; and X, X' are independently -NH, -NR''', O or S, in a physiologically acceptable carrier.

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19. A method according to claim 18, wherein Z is



20. A method according to claim 19, wherein Z is H.

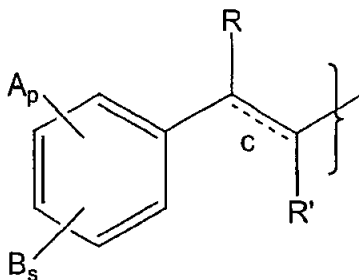
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21. A method according to claim 18, wherein Z is A''.

22. A method according to claim 18, wherein Z is B''.

15

23. A method according to claim 18, wherein Z is



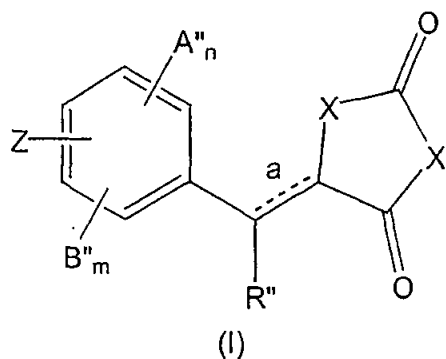
24. A method according to claim 18, wherein R'', A'', B'', A'_q, B', A_p and R are all hydrogen, X is sulfur and X' is NH.

25. A method according to claim 18, wherein R'' is carbomethoxy
5 and B is methoxy and s is 2.

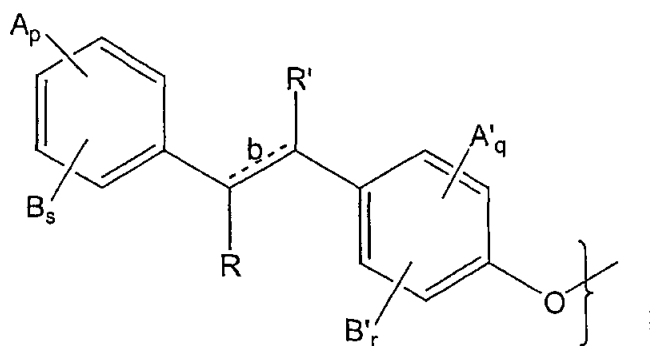
26. A method according to claim 18, wherein said compound is 5-(4-(4-(1-carbomethoxy-2-)3,5-dimethoxy phenyl) ethenyl)-phenoxy)-benzyl)-2,4-thiazolidinedione.

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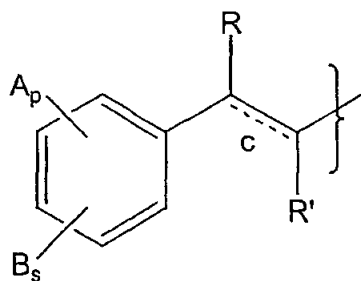
27. A method of treating inflammation comprising the steps of administering to a subject suffering from an inflammatory condition, a therapeutically effective amount of a compound according to the formula I:



wherein Z is



H; A''; B''; or



- n, m, q and r are independently integers from zero to 4 provided that $n + m \leq 4$ and $q + r \leq 4$; p and s are independently integers from zero to 5 provided that $p + s \leq 5$; a, b and c are double bonds which may be present or absent; when present, the double bonds may be in the E or Z configuration and, when absent, the resulting stereocenters may have the R- or S- configuration;

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R, R' and R'' are independently H, C₁-C₂₀ linear or branched alkyl, C₂-C₂₀ linear or branched alkenyl, -CO₂Z', where Z' is H, sodium, potassium, or other pharmaceutically acceptable counter-ion such as calcium, magnesium, ammonium, tromethamine, and the like; -CO₂R''', -NH₂, -NHR''', -NR₂'', -OH, -OR''', halo, substituted C₁-C₂₀ linear or branched alkyl or substituted C₂-C₂₀ linear or branched alkenyl, wherein R''' is C₁-C₂₀ linear or branched alkyl or linear or branched alkenyl;

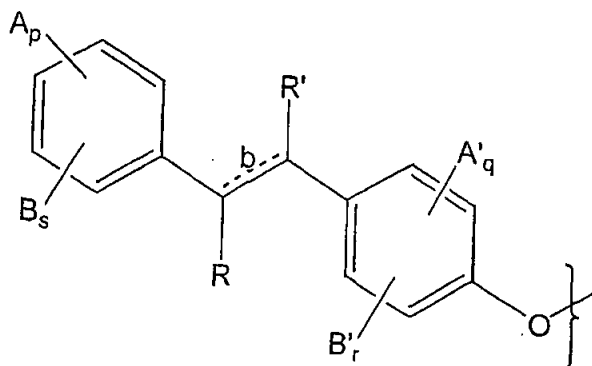
10 A, A' and A'' are independently H, C₁-C₂₀ acylamino;
 C₁-C₂₀ acyloxy; C₁-C₂₀ alkanoyl;
 C₁-C₂₀ alkoxycarbonyl; C₁-C₂₀ alkoxy;
 C₁-C₂₀ alkylamino; C₁-C₂₀ alkylcarboxylamino; carboxyl; cyano;
 halo; hydroxy;

15 B, B' and B'' are independently H;
 C₁-C₂₀ acylamino; C₁-C₂₀ acyloxy; C₁-C₂₀ alkanoyl;
 C₁-C₂₀ alkenoyl; C₁-C₂₀ alkoxycarbonyl;
 C₁-C₂₀ alkoxy; C₁-C₂₀ alkylamino;
 C₁-C₂₀ alkylcarboxylamino; aroyl, aralkanoyl; carboxyl; cyano; halo;

20 hydroxy;
 or A and B together, or A' and B' together, or A'' and B'' together, may be joined to form a methylenedioxy or ethylenedioxy group; and
 X, X' are independently -NH, -NR''', O or S,
 in a physiologically acceptable carrier.

25

28. A method according to claim 27, wherein Z is



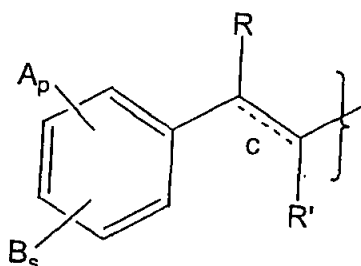
29. A method according to claim 27, wherein Z is H.

5 30. A method according to claim 27, wherein Z is A''.

31. A method according to claim 27, wherein Z is B''.

32. A method according to claim 27, wherein Z is

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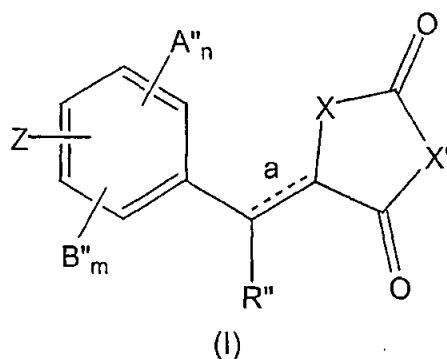
33. A method according to claim 27, wherein R'', A'', B'', A'_q, B'_r, A_p and R are all hydrogen, X is sulfur and X' is NH.

15 34. A method according to claim 33, wherein R' is carbomethoxy and B is methoxy and s is 2.

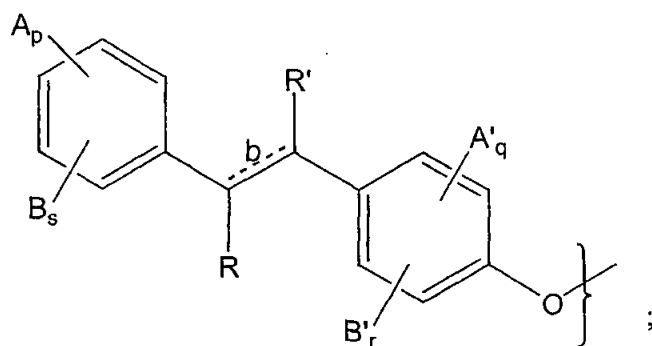
35. A method according to claim 27, wherein said compound is 5-(4-(4-(1-carbomethoxy-2-)3,5-dimethoxy phenyl) ethenyl)-phenoxy)-benzyl)-2,4-thiazolidinedione.

5 36. A method of treating immunological disease comprising the steps of administering to a subject suffering from an immunological disease, a therapeutically effective amount of a compound according to the formula I:

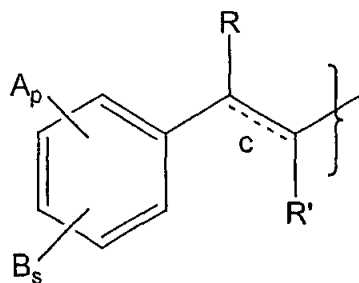
7C



wherein Z is



H; A''; B''; or



- n, m, q and r are independently integers from zero to 4 provided that $n + m \leq 4$ and $q + r \leq 4$; p and s are independently integers from zero to 5 provided that $p + s \leq 5$; a, b and c are double bonds which may be present or absent;
 5 when present, the double bonds may be in the E or Z configuration and when absent, the resulting stereocenters may have the R- or S- configuration;

R, R' and R'' are independently H, C₁-C₂₀ linear or branched alkyl, C₂-C₂₀ linear or branched alkenyl, -CO₂Z', where Z' is H, sodium, potassium, or other pharmaceutically acceptable counter-ion such as calcium, magnesium, ammonium, tromethamine, and the like; -CO₂R''', -NH₂, -NHR''', -NR₂'', -OH, -OR''', halo, substituted C₁-C₂₀ linear or branched alkyl or substituted C₂-C₂₀ linear or branched alkenyl, wherein R''' is C₁-C₂₀ linear or branched alkyl or linear or branched alkenyl;

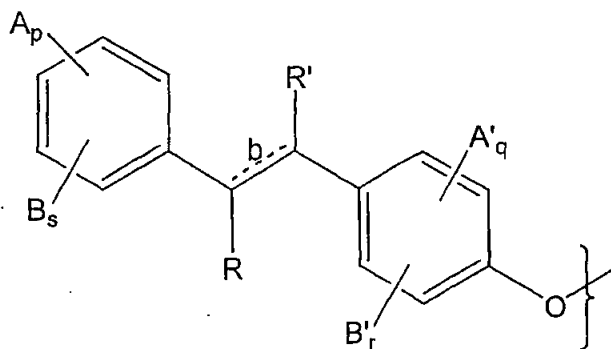
A, A' and A'' are independently H, C₁-C₂₀ acylamino;
 C₁-C₂₀ acyloxy; C₁-C₂₀ alkanoyl;
 C₁-C₂₀ alkoxy; C₁-C₂₀ alkoxy; C₁-C₂₀ alkoxy;
 C₁-C₂₀ alkylamino; C₁-C₂₀ alkylcarboxylamino; carboxyl; cyano;
 halo; hydroxy;

B, B' and B'' are independently H;
 C₁-C₂₀ acylamino; C₁-C₂₀ acyloxy; C₁-C₂₀ alkanoyl;
 C₁-C₂₀ alkenoyl; C₁-C₂₀ alkoxy; C₁-C₂₀ alkoxy;
 C₁-C₂₀ alkylamino; C₁-C₂₀ alkylamino;
 C₁-C₂₀ alkylcarboxylamino; aroyl, aralkanoyl; carboxyl; cyano; halo;
 hydroxy;

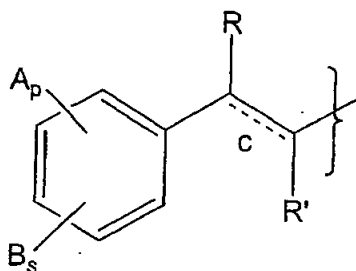
or A and B together, or A' and B' together, or A'' and B'' together, may be joined to form a methylenedioxy or ethylenedioxy group; and
 X, X' are independently -NH, -NR''', O or S,
 in a physiologically acceptable carrier.

37. A method according to claim 36, wherein Z is

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38. A method according to claim 36, wherein Z is H.
39. A method according to claim 36, wherein Z is A''.
40. A method according to claim 36, wherein Z is B''.
41. A method according to claim 36, wherein Z is



42. A method according to claim 36, wherein R'', A'', B'', A'_q, B', A_p and R are all hydrogen, X is sulfur and X' is NH.
43. A method according to claim 42, wherein R' is carbomethoxy and B is methoxy and s is 2.

44. A method according to claim 36, wherein said compound is 5-(4-(4-(1-carbomethoxy-2-)3,5-dimethoxy phenyl) ethenyl)-phenoxy)-benzyl)-2,4-thiazolidinedione.

5 45. A method of inhibiting the activity of TNF-alpha, IL-1, IL-6 or COX-2 which comprises administering to a host in need of such inhibition an effective amount of a compound according to claim 1.

10 46. The method of treating inflammation, inflammatory or immunological disease which comprises administering to a host in need of such treatment an effective amount of a compound according to claim 1.

15 47. The method of inhibiting the undesired action of cytokine or cyclooxygenase which comprises administering to a host in need of such inhibition an effective amount of a compound according to claim 1.

20 48. The method of treating an inflammatory disease mediated by cytokines or cyclooxygenase which comprises administering to a host in need of such treatment a compound according to claim 1.

49. The method of treating insulin resistance which comprises administering to a host in need of such treatment an effective amount of a compound according to claim 1.

25 50. The method of treating hyperlipidemia which comprises administering to a host in need of such treatment an effective amount of a compound according to claim 1.

30 51. The method of treating coronary heart disease which comprises administering to a host in need of such treatment an effective amount of a compound according to claim 1.

52. The method of treating multiple sclerosis which comprises administering to a host in need of such treatment an effective amount of a compound according to claim 1.

5

53. The method of treating cancer which comprises administering to a host in need of such treatment an effective amount of a compound according to claim 1.

10

54. The method of claim 45, 46, 47, 48, 49, 50, 51, 52 or 53 wherein the compound is 5-(4-(4-(1-carbomethoxy)-2-(3,5-dimethoxyphenyl)-ethenyl)-phenoxy)-benzyl)-2,4-thiazolidinedione.

15

55. A compound according to claim 1 selected from the group consisting of:

3-(3,5-dimethoxyphenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-acrylic acid,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-acrylamide,

20

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-N,N-dimethyl-acrylamide,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-N-methoxy,-N-methyl-acrylamide,

25

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-phenyl}-propionic acid methyl ester,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-phenyl}-acrylic acid methyl ester,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-propionic acid,

30

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-phenyl}-propionic acid,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-
phenoxy]-phenyl}-acrylic acid, and
3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-
phenyl}-propionic acid methyl ester.

5

56. A compound according to claim 1 which is 3-(3,5-dimethoxyphenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-acrylic acid.

10

57. A pharmaceutical composition comprising a therapeutically effective amount of a compound selected from the group consisting of 3-(3,5-dimethoxyphenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-acrylic acid,

15

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-acrylamide,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-N,N-dimethyl-acrylamide,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-N-methoxy,-N-methyl-acrylamide,

20

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-phenyl}-propionic acid methyl ester,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-phenyl}-acrylic acid methyl ester,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-propionic acid,

25

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-phenyl}-propionic acid,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-phenyl}-acrylic acid, and

30

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-propionic acid methyl ester,

together with a physiologically acceptable carrier therefor.

58. The pharmaceutical composition of claim 57 wherein said compound is 3-(3,5-dimethoxyphenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-acrylic acid.

59. The method of claim 18, 45, 46, 47, 48, 49, 50, 51, 52 or 53 wherein said compound is selected from the group consisting of

3-(3,5-dimethoxyphenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-acrylic acid,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-acrylamide,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-N,N-dimethyl-acrylamide,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-N-methoxy,-N-methyl-acrylamide,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-phenyl}-propionic acid methyl ester,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-phenyl}-acrylic acid methyl ester,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-propionic acid,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-phenyl}-propionic acid,

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-phenyl}-acrylic acid, and

3-(3,5-dimethoxy-phenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-propionic acid methyl ester.

79

60. The method of claim 59 wherein the compound is 3-(3,5-dimethoxyphenyl)-2-{4-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-phenyl}-acrylic acid.

5

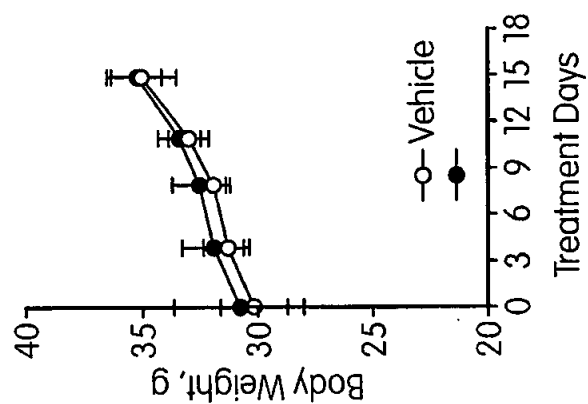


FIG. 1B

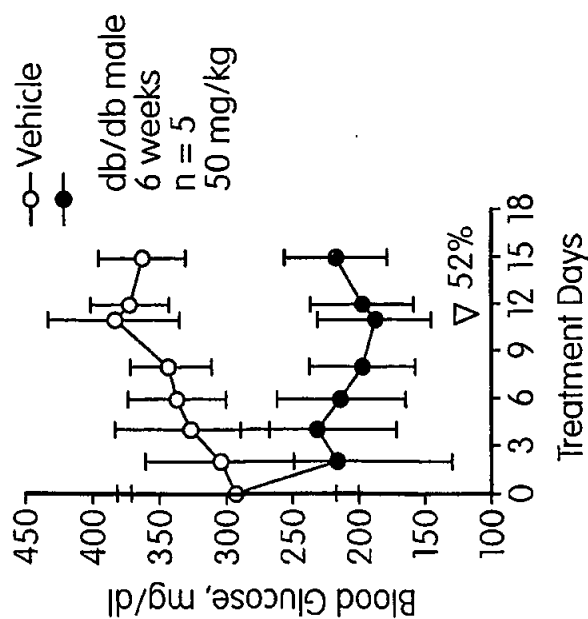


FIG. 1A

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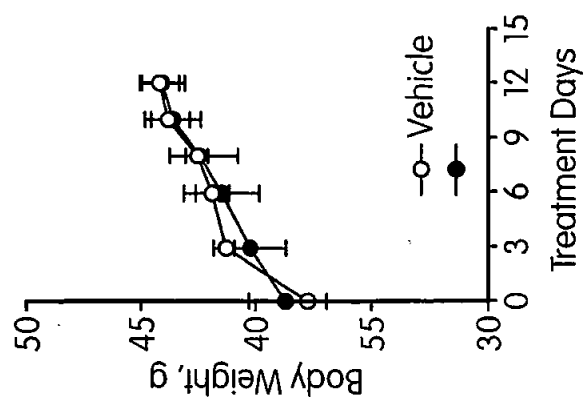


FIG. 2B

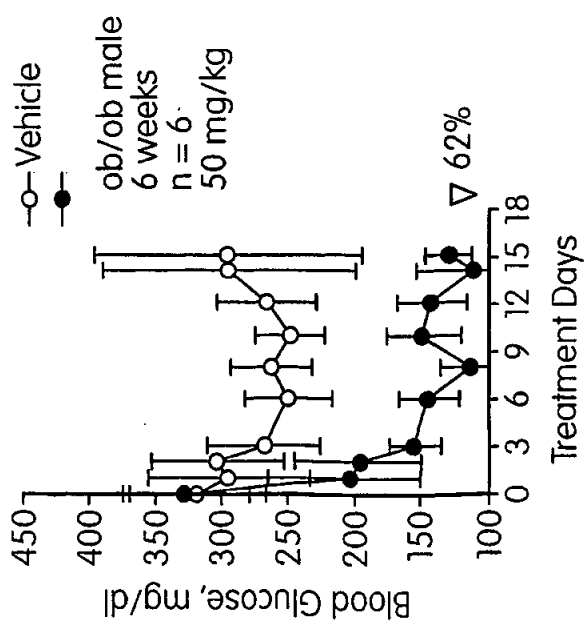


FIG. 2A

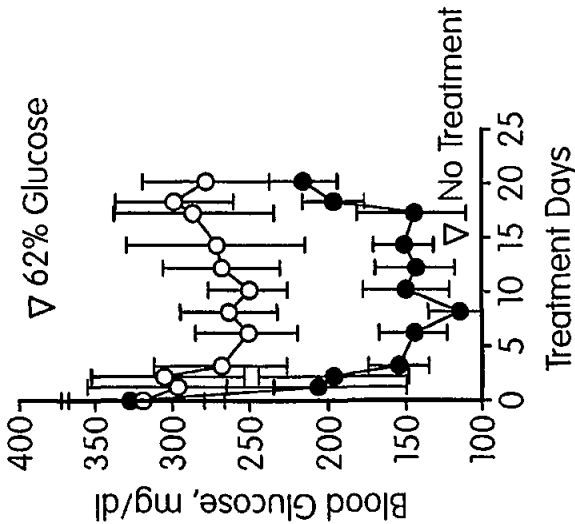


FIG. 3B

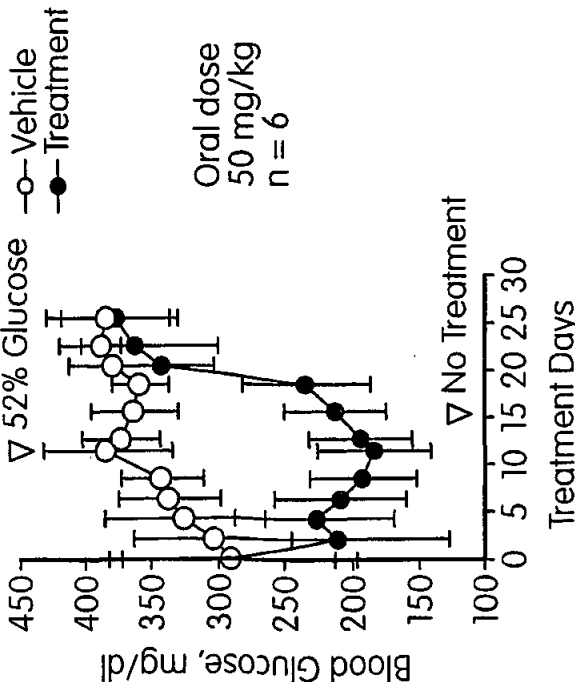


FIG. 3A

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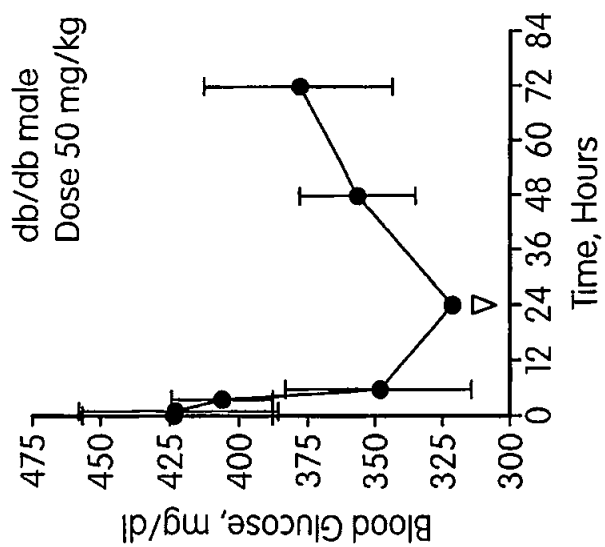


FIG. 4

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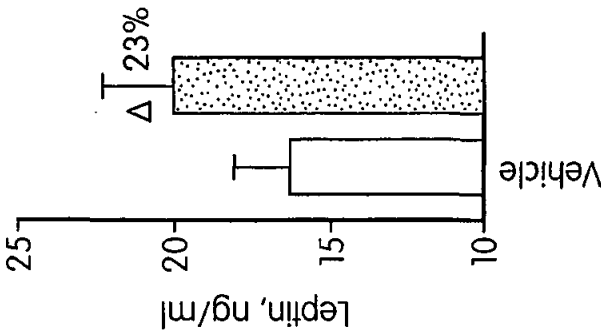


FIG. 5D

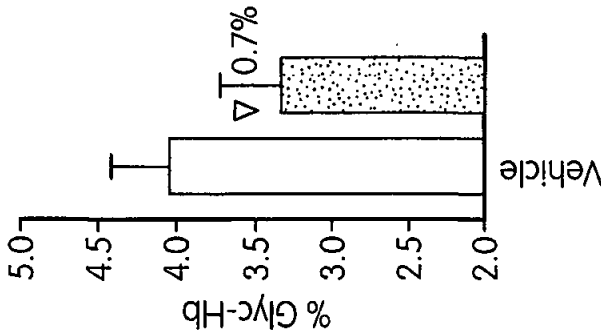


FIG. 5C

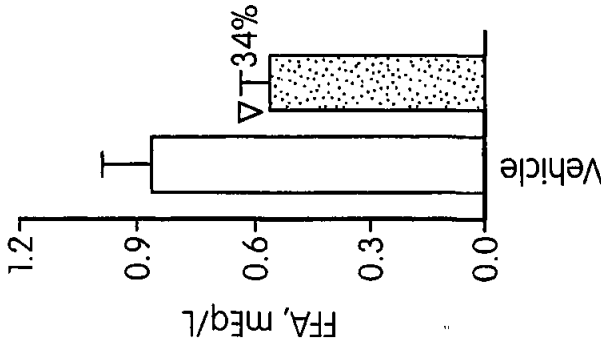


FIG. 5B

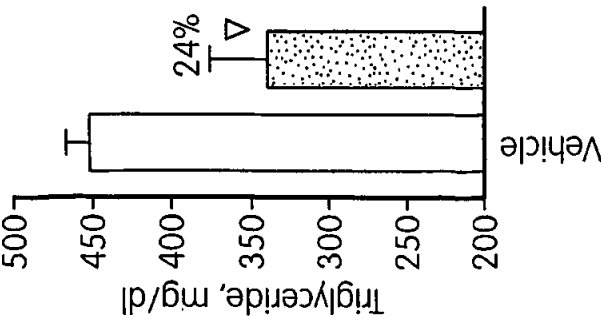


FIG. 5A

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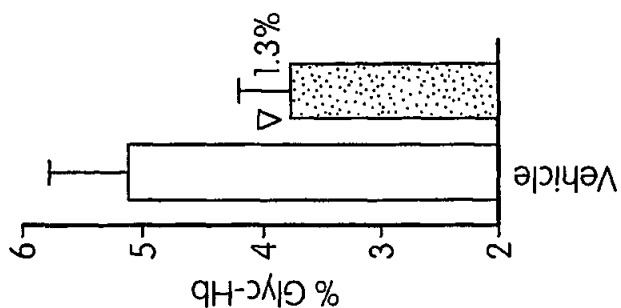


FIG. 6D

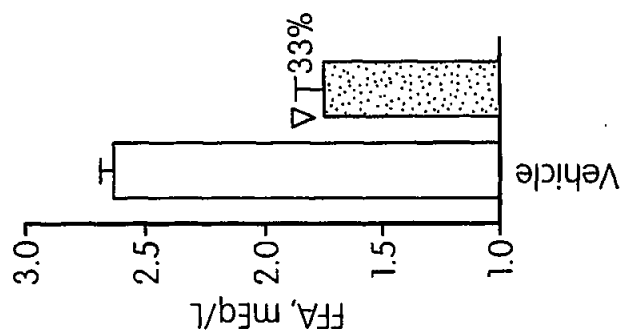


FIG. 6C

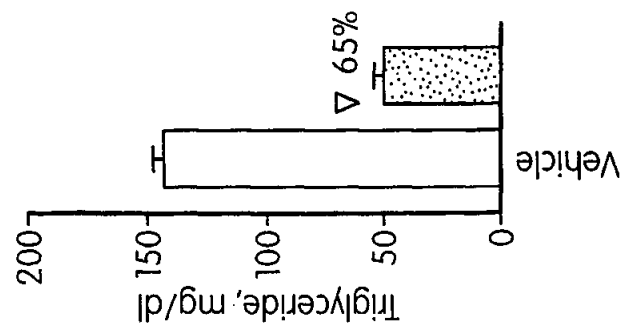


FIG. 6B

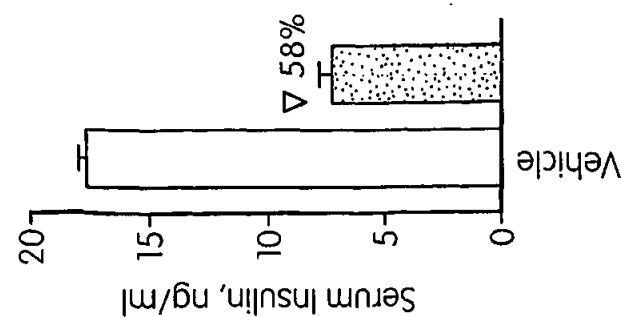


FIG. 6A

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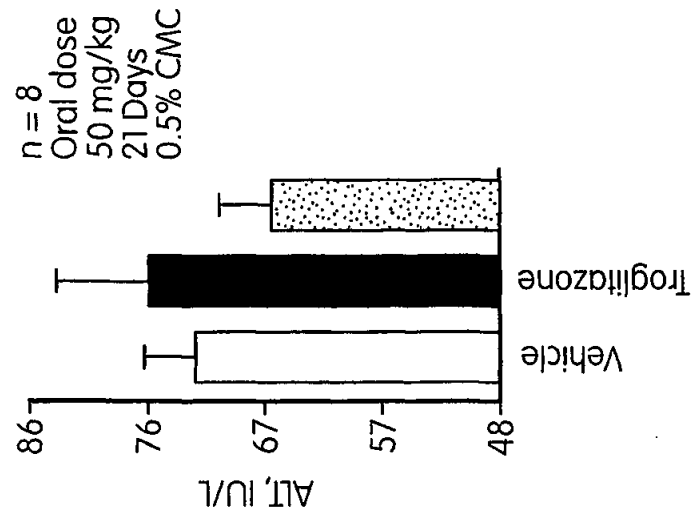


FIG. 7B

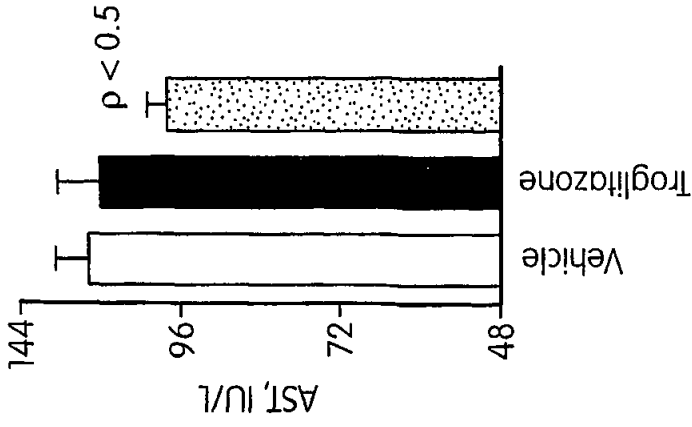


FIG. 7A

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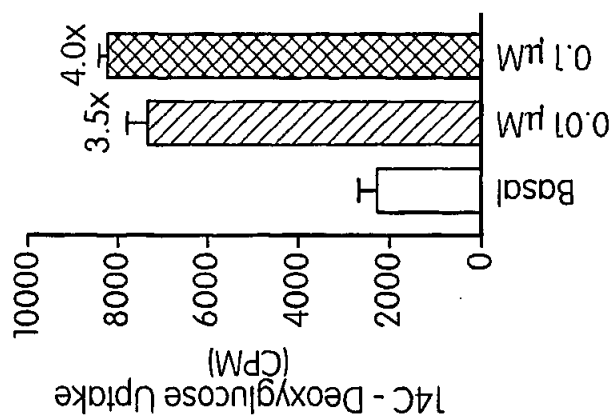


FIG. 8

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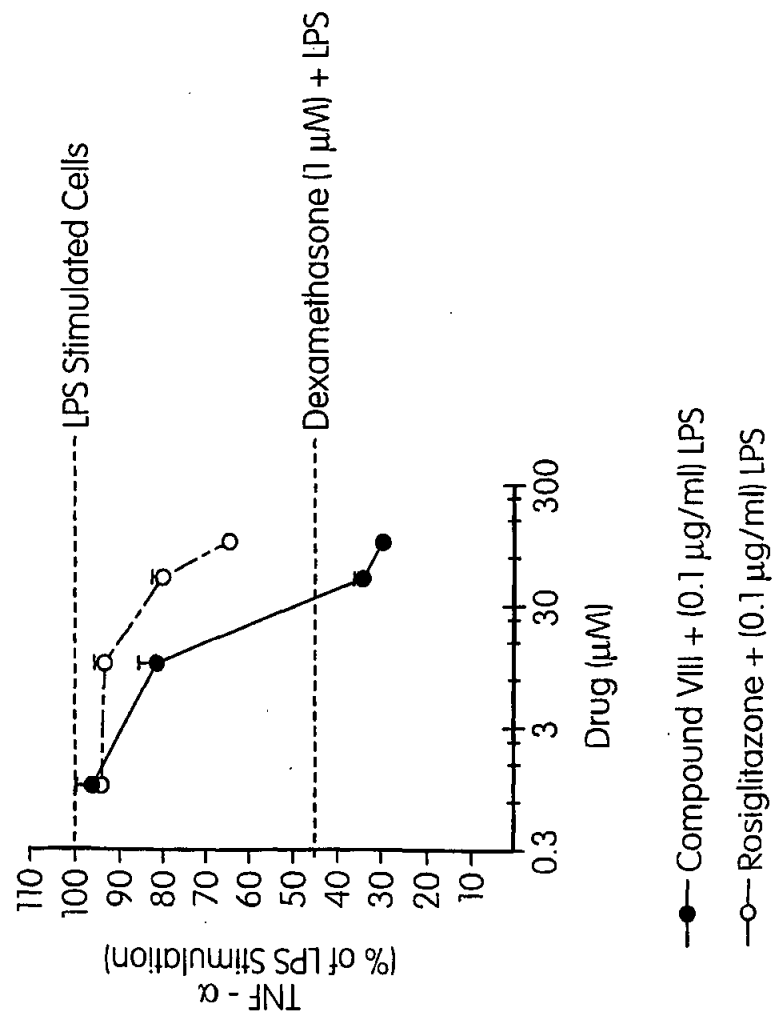


FIG. 9

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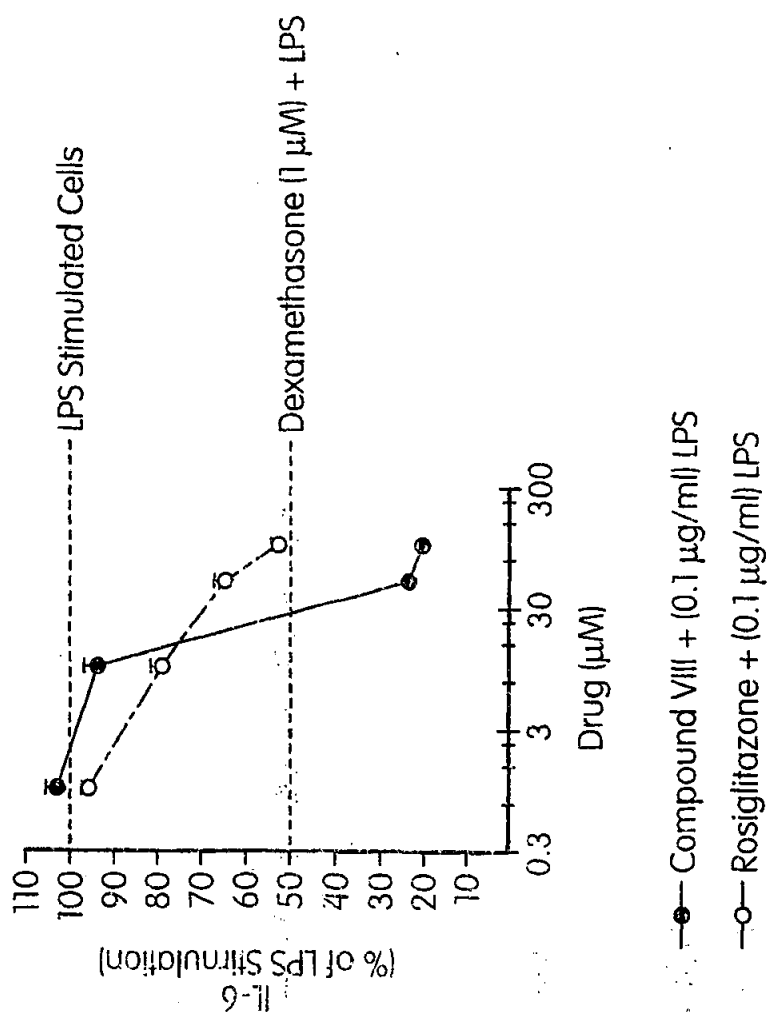
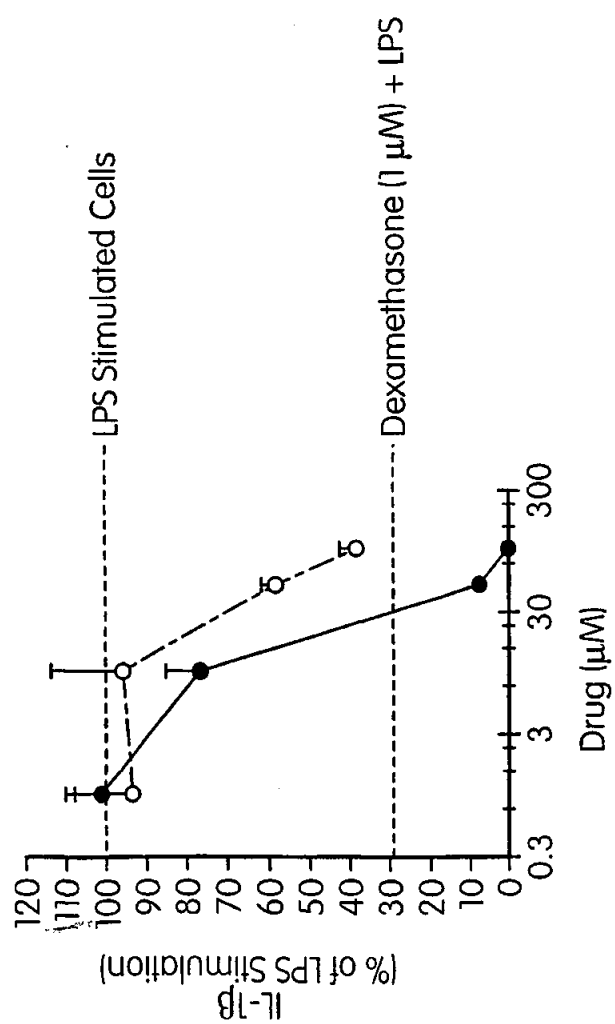


FIG. 10

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—●— Compound VIII + (0.1 μg/ml) LPS
—○— Rosiglitazone + (0.1 μg/ml) LPS

FIG. 11

9.1

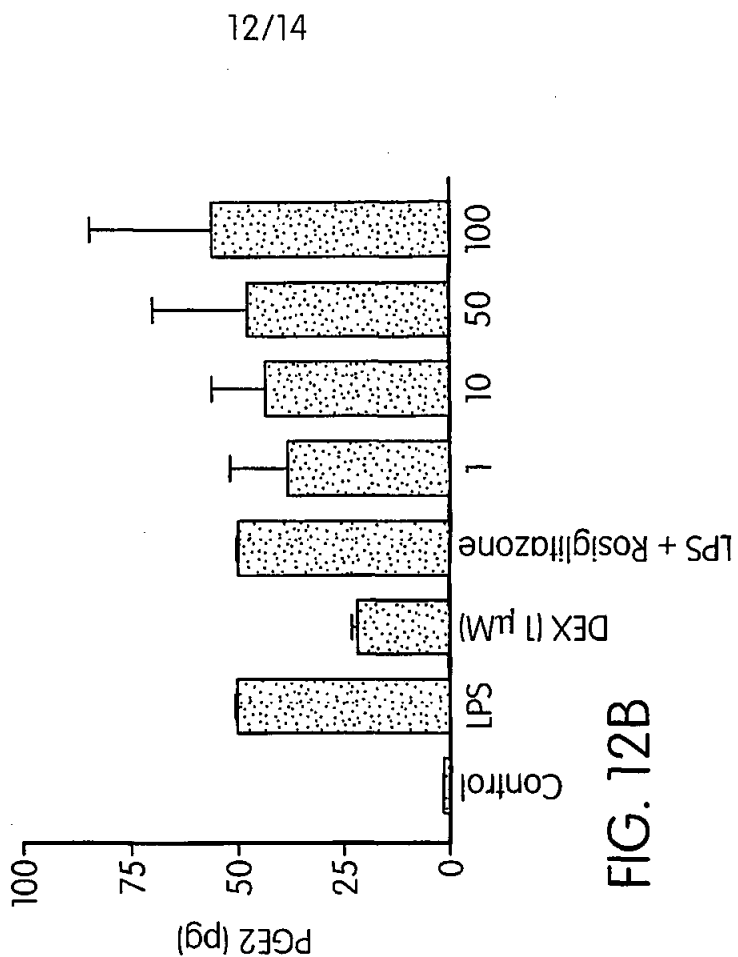


FIG. 12B

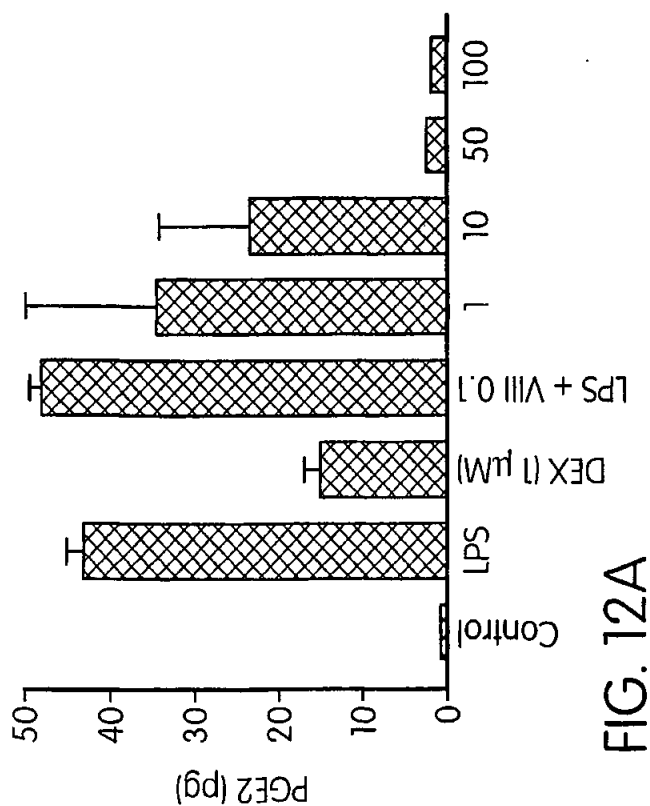
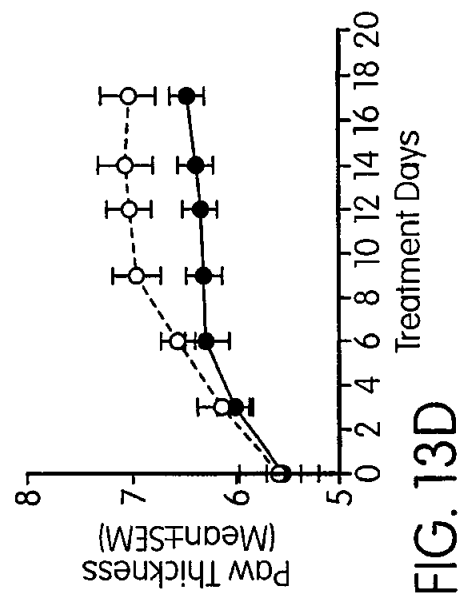
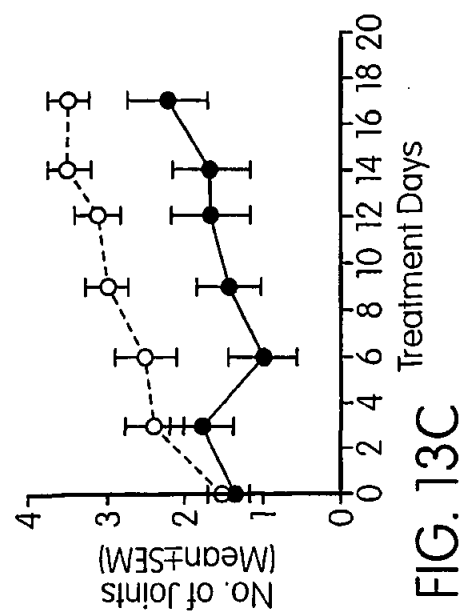
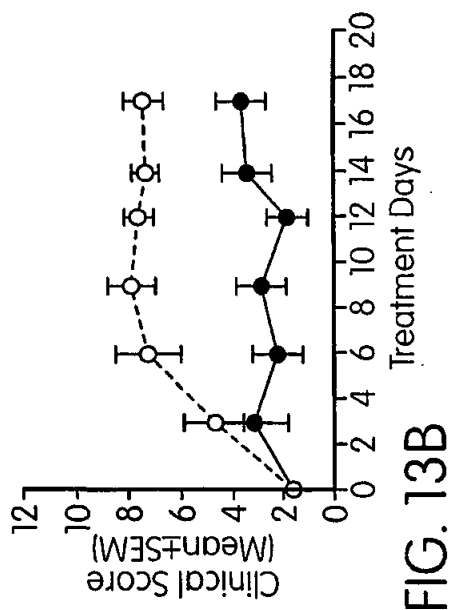
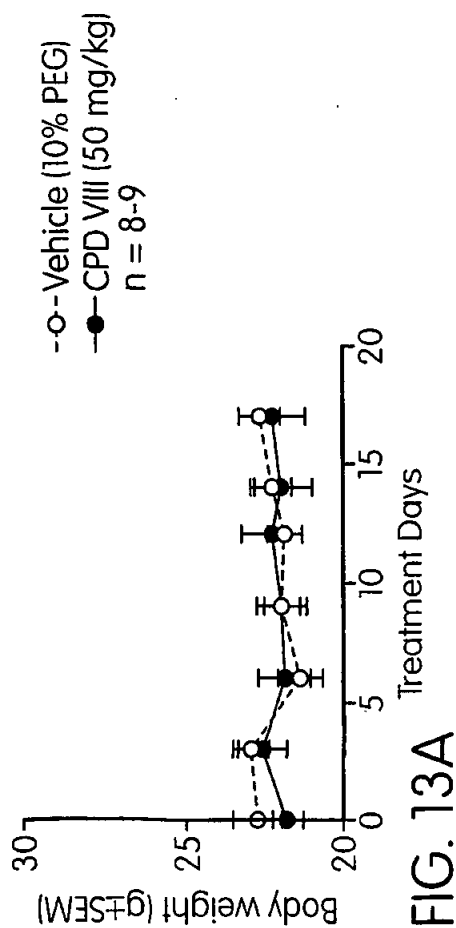


FIG. 12A

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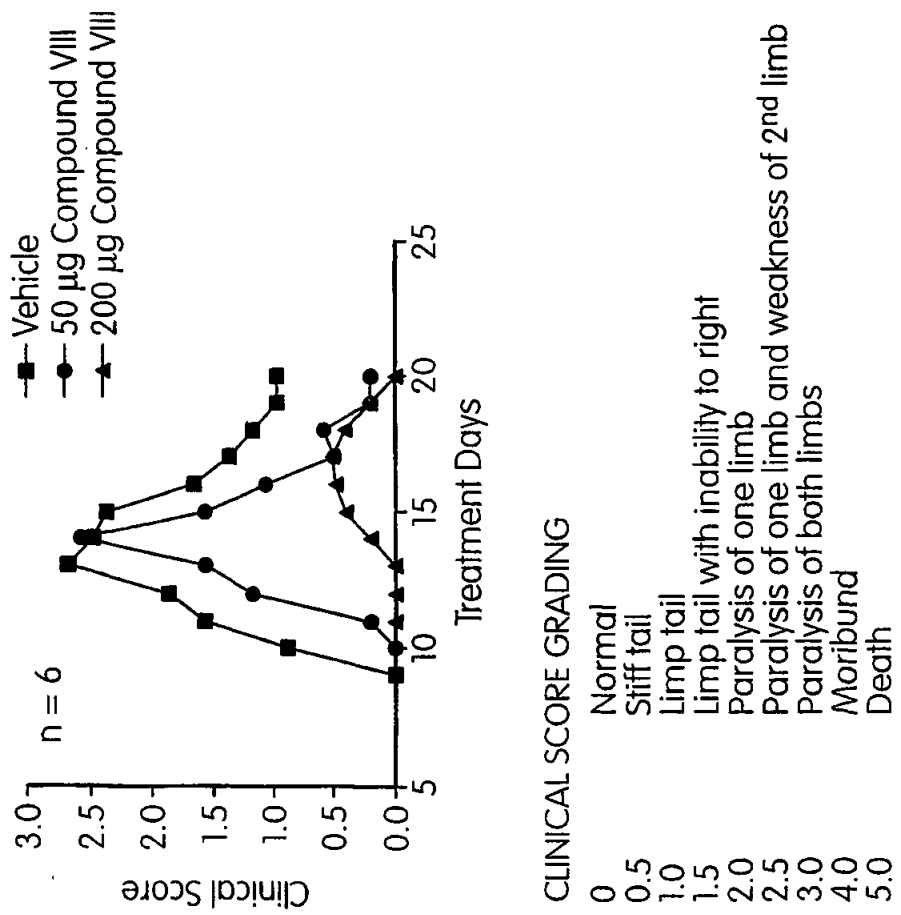


FIG. 14

Anexo 2

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(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

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



WO 02/05791 A2

(54) Title: ANTTUMOR COMBINED THERAPY

(57) Abstract: A method of treating a human being suffering from a hormone-dependent disorder characterized by the overexpression of EGFR, comprising administering to said human being an aromatase inhibitor and an EGFR antagonist or EGFR inhibitor, in amounts effective to produce a superadditive or synergistic therapeutic effect.

ANTITUMOR COMBINED THERAPY

The present invention concerns the treatment of estrogen
5 dependent disorders characterized by the overexpression of
EGFR. More specifically, the invention concerns the
treatment of a human being susceptible to or diagnosed with
a disorder characterized by the overexpression of EGFR with
a combination of an EGFR antagonist or inhibitor and an
10 aromatase inhibitor.

The utility of aromatase inhibitors; EGFR antagonists and
EGF inhibitors is well acknowledged in anticancer therapy.
However, it is also well known in the art that
administration to a patient of therapeutically effective
15 amounts of aromatase inhibitors can cause considerable side
effects. The major toxicities are for instance lethargy,
hot flashes, rash, transient leukopenia, dizziness, nausea,
constipation and vomiting. On the other hand, also
administration to a patient of therapeutically effective
20 amounts of an EGFR antagonist or inhibitor can similarly
cause considerable side effects, e.g. hypersensitivity,
alterations of renal function, myocardial lesions and
cardiotoxicity in general.

25 The inventors of the present invention have found that a
combination therapy of an hormone, in particular estrogen,
dependent disorder characterized by the overexpression of
EGFR, comprising a therapeutically effective amount of an
aromatase inhibitor and a therapeutically effective amount
30 of an EGFR antagonist or inhibitor, can produce a
therapeutic effect which is greater than that obtainable by
single administration of a therapeutically effective amount
of either a sole aromatase inhibitor or a sole EGFR
antagonist or inhibitor.

Similarly they have found that a combination therapy of an hormone, in particular estrogen, dependent disorder characterized by the overexpression of EGFR, comprising a therapeutically sub-effective amount of an aromatase inhibitor and a therapeutically sub-effective amount of an EGFR antagonist or inhibitor, can produce substantially the same therapeutic effect, which is obtainable by single administration of a therapeutically effective amount of either an aromatase inhibitor or an EGFR antagonist or inhibitor. The most important, they have found that such newly obtained therapeutic effect is not paralleled by the toxic effects, otherwise caused by single administrations of either therapeutically effective amounts of an aromatase inhibitor or therapeutically effective amounts of an EGFR antagonist or inhibitor.

In view of the above, the effectiveness of an aromatase inhibitor and an EGFR antagonist or inhibitor is significantly increased without a parallel increased toxicity. In other words, the combined therapy of the present invention enhances the therapeutic effects of the aromatase inhibitor and the EGFR antagonist or inhibitor and thus yields more effective and less toxic treatment for hormone-dependent disorders.

Accordingly, the present invention provides a new and valuable tool in the therapy of hormone dependent disorders characterized by the overexpression of EGFR. The advantages provided by the present invention can be appreciated by their preferred features, described herebelow.

Examples of such disorders are cancers, e.g. breast, cervical, ovarian and endometrial cancers. However a preferred example of such disorders is breast cancer in a human being, in particular a female.

Accordingly, the present invention provides, as a first object, a pharmaceutical composition comprising an aromatase inhibitor and an EGFR antagonist or inhibitor, having a synergistic or superadditive therapeutic activity
5 against an hormone-dependent disorder characterized by the overexpression of EGFR.

The present invention also provides the use of an aromatase inhibitor in the manufacture of a pharmaceutical
10 composition for treatment of an hormone-dependent disorder characterized by the overexpression of EGFR, the treatment additionally comprising the administration of a composition comprising an EGFR antagonist or inhibitor, in amounts effective to produce a superadditive effect.

15

Examples of aromatase inhibitors according to the invention are exemestane, aminoglutethimide, roglethimide, pyridoglutethimide, anastrozole, trilostane, testolactone, formestane, atamestane, 1-methyl-1,4-androstadiene-3,17-
20 dione (MAD), ketokonazole, fadrozole, letrozole, vorozole and anastrozole.

Preferred examples of aromatase inhibitors according to the invention are exemestane, anastrozole and letrozole, in particular exemestane.

25 The aromatase inhibitors cited herein are well known products, which are cited for instance in Cancer-Treat-Res.: 94, 231-254, 1998 and WO 99/30708.

An EGFR inhibitor is for instance compound ZM 105180, compound CP 358774 or compound ZD 1839. Compound ZM 105180
30 is 6-amino-4-(3-methylphenyl-amino)-quinazoline which is known from WO 95/03283. Compound CP 358774 is N-(3-ethylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, which is known from WO 96/30347. Compound ZD 1839 is N(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)-
35 propoxy]4-quinazolinamine, which is known from WO 96/33980.

Alternatively, an EGFR antagonist is for instance an antibody.

An antibody against EGFR, according to the invention, can be either an "intact" antibody or a fragment thereof.

5 The term "antibody" is used in the broadest sense and specifically covers intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g. bispecific antibodies) formed from at least two intact antibodies, and antibody fragments so long as they exhibit
10 the desired biological activity. "Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies; single-
15 chain antibody molecules; and multispecific antibodies formed from antibody fragments.

An antibody against EGFR is in particular chimerized antibody C225 (cetuximab) and human antibodies E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 and E7.6.3, in particular
20 E7.6.3. Preferred antibodies against EGFR are chimerized antibody C225 and human antibody E7.6.3. Chimerized antibody C225 is disclosed by WO 94/49210. Human antibodies E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 and E7.6.3 are disclosed by WO 98/50433.

25 The present invention also provides a product comprising an aromatase inhibitor and an EGFR antagonist or inhibitor, as combined preparation for simultaneous, separate or sequential administration, in amounts to produce a
30 synergistic or superadditive therapeutic activity against an hormone-dependent disorder characterized by the overexpression of EGFR.

In a further aspect, the present invention provides a kit
35 comprising, in a suitable container means, a pharmaceutical

composition containing an aromatase inhibitor, as an active agent, and an EGFR antagonist or inhibitor, as a further active agent, in amounts to produce a synergistic or superadditive therapeutic activity against hormone-
5 dependent disorder characterized by the overexpression of EGFR.

A further aspect of the present invention is to provide a method of treating a human being, particularly a female,
10 suffering from an hormone-dependent disorder characterized by the overexpression of EGFR comprising administering to said human being an aromatase inhibitor and an EGFR antagonist or inhibitor, in amounts effective to produce a superadditive or synergistic therapeutic effect.

15 A still further aspect of the present invention is to provide a method for lowering the side effects (adverse reactions) caused by antitumor therapy with an aromatase inhibitor in a human being, particularly a female,
20 suffering from an hormone-dependent tumor overexpressing EGFR, the method comprising administering to said human being a combined preparation comprising an aromatase inhibitor and an EGFR antagonist or inhibitor, in amounts effective to produce a superadditive or synergistic
25 antitumor effect, while controlling the growth of neoplasm formation.

A still further aspect of the present invention is to provide a method for lowering the side effects (adverse
30 reactions) caused by antitumor therapy with an EGFR antagonist or inhibitor in a human being, particularly a female, suffering from an hormone-dependent tumor overexpressing EGFR, the method comprising administering to said human being a combined preparation comprising an EGFR
35 antagonist or inhibitor and an aromatase inhibitor, in

amounts effective to produce a superadditive or synergistic antitumor effect, while controlling the growth of neoplasm formation.

5 The combination preparation according to the invention can also include combination packs or compositions in which the constituents are placed side by side and can be administered simultaneously, separately or sequentially to one and the same human being. Accordingly, the aromatase
10 inhibitor and the EGFR antagonist or inhibitor may be present within a single or distinct container.

By the term "a superadditive or synergistic antitumor effect" as used herein is meant the inhibition of the
15 growth tumor, preferably the complete regression of the tumor, by administering a combination of an aromatase inhibitor, as defined above, and an EGFR antagonist or inhibitor, to a human being, particularly a human female. Said preparation having therefore a potentiated antitumor
20 (superadditive) activity with respect to products containing either an aromatase inhibitor or an EGFR antagonist or inhibitor, which is greater than the sum of the actions of individual components.

By the term "administered" or "administering" as used
25 herein is meant any acceptable manner of administering a drug to a patient which is medically acceptable including parenteral and oral administration. Preferably the aromatase inhibitor and the EGFR antagonist or inhibitor are administered in a sequential, separate or substantially
30 simultaneous manner.

By "parenteral" is meant intravenous, subcutaneous, intradermal or intramuscular administration.

Oral administration includes administering the constituents of the combined preparation in a suitable oral form such
35 as, e.g., tablets, capsules, suspensions, solutions,

emulsions, powders, syrups and the like.

Parenteral administration includes administering the constituents of the combined preparation by subcutaneous, subcutaneous, intravenous or intramuscular injections.

5

The actual preferred method and order of administration of the combined preparations of the invention may vary according to, inter alia, the particular pharmaceutical formulation of the aromatase inhibitor being utilized, the particular pharmaceutical formulation of the EGFR antagonist or inhibitor being utilized, the particular cancer being treated and the particular patient being treated.

The dosage ranges for the administration of the combined preparation may vary with the age, condition and extent of the disease in the patient and can be determined by one of skill in the art.

The dosage regimen must therefore be tailored to the particular of the patient's conditions, response and associate treatments in a manner which is conventional for any therapy, and may need to be adjusted in response to changes in conditions and/or in light of other clinical conditions.

In the combined method of treatment according to the subject invention, the aromatase inhibitor may be administered simultaneously with the EGFR antagonist or inhibitor or the compounds may be administered sequentially, in either order.

An effective amount of an aromatase inhibitor antitumor agent may vary from about 0.5 to about 500 mg pro dose 1-2 times a day. Exemestane, for example, may be administered orally in a dosage range varying from about 5 to about 200 mg, and particularly, from about 10 to about 25 mg, or parenterally from about 50 to about 500 mg, in particular from about 100 to about 250 mg.

Fadrozole, for example, may be administered orally in a dosage range varying from about 0.5 to about 10 mg, and particularly, from about 1 to about 2 mg.

5 Letrozole, for example, may be administered orally in a dosage range varying from about 0.5 to about 10 mg, and particularly, from about 1 to about 2.5 mg.

Formestane, for example, may be administered parenterally in a dosage range varying from about 250 to about 500 mg, and particularly, from about 250 to about 300 mg.

10 Anastrozole, for example, may be administered orally in a dosage range varying from about 0.5 to about 10 mg, and particularly, from about 1 to about 2 mg.

In the method of the subject invention, for example for the administration of the recombinant humanized monoclonal
15 antibody anti-EGFR C225 (cetuximab), the course of therapy generally employed is from about 150 to about 500 mg/m² of body surface area. Preferably, the course therapy employed consists of a loading dose of about 400 mg/m², followed by weekly maintenance dosage of about 180-250 mg/m². According
20 to a preferred embodiment of the invention patients are given an injection of cetuximab as a weekly, dose escalating 4-week protocol, with doses up to 200 mg/m². If the disease is stabilized, then a further 8-week course can begin.

25 In the method of the subject invention, for the administration e.g. of the recombinant humanized monoclonal antibody E7.6.3 the course of therapy generally employed is from about 1 to about 1000 mg/m² of body surface area. More preferably, the course therapy employed is from about 60 to
30 about 600 mg/m² of body surface area.

In the method of the subject invention, for the administration e.g. of compound CP-358774 the course of therapy generally employed is from about 25 to about 150 mg/day p.o.s., so that to reach a plasma concentration from
35 about 300 to about 700 ng/ml, preferably 500 ng/ml.

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In the method of the subject invention, for the administration e.g. of compound ZD 1839 the course of therapy generally employed is from about 50 to about 300 mg/day p.os.

5 The therapy method according to the present invention is, in particular, suitable for treating a human being suffering from hormone dependent disorders, characterized by the overexpression of EGFR. Typical examples of such disorders are tumors, like ovarian, cervical and
10 endometrial cancers in a human female or breast cancer in a human being, in particular a female.

More in particular, the combined use of an aromatase inhibitor, according to the invention, preferably exemestane, and an EGFR antagonist, for example antibody
15 C225 or E7.6.3 or an EGFR inhibitor, e.g. compounds CP-358774, ZD 1839 or ZM 105180, can be suitable for the treatment of patients with cancers over-expressing EGFR, for example, for patient with breast cancer, in particular with metastatic breast cancer, over-expressing EGFR.

20 According to a preferred aspect of the present invention the superadditive antitumor effect results in an anti breast cancer therapy having increased effectiveness in controlling, i.e. slowing, interrupting, arresting, stopping or reversing, the neoplasm formation.

25 As used herein, "controlling the growth" of the neoplasm refers to slowing, interrupting, arresting or stopping its growth and it does not necessarily indicate a total elimination of the neoplasm.

Therefore, the term "treating" simply means that the life
30 expectancy of an individual affected with a cancer will be increased, that one or more of the symptoms of the disease will be reduced and/or that quality of life will be enhanced.

The compositions and combined therapy method of the
35 invention provide therefore a two-way attack in particular

on cancer cell growth. Exemestane in view of its biological properties, is the most preferred example of aromatase inhibitor according to the invention.

From the pharmacological point of view, the valuable
5 biological properties of exemestane may be found in its peculiar mechanism of aromatase inactivation.

The aromatase enzyme (450_{arom}) is a specific form of cytochrome P450 hemoprotein composed of a P450 (heme) moiety and a peptidic moiety. The enzyme catalyzes a
10 multistep reaction leading to aromatization of the A ring of the androgen substrate (mainly androstenedione) to estrone, requiring the presence of the cofactor NADPH. After this enzymatic reaction, the enzyme molecule is once more available to perform a new aromatization.

15 The exemestane's mechanism of aromatase inhibition has been extensively studied and the compound has been found to cause enzyme inactivation. In fact exemestane, structurally related to the natural substrate androstenedione, is initially recognized by the aromatase enzyme as a false
20 substrate, therefore competes with androstenedione at the active site of the enzyme. The compound is then transformed (through and NADPH-dependent mechanism) to an intermediate which binds irreversibly to the enzyme causing its inactivation (also known as suicide inhibition). Therefore
25 the enzyme is definitely inactivated and de novo enzyme synthesis is required for oestrogen production.

Suitable modifications and adaptations of a variety of conditions and parameters normally encountered in clinical therapy which are obvious to those skilled in the art are
30 within the scope of this invention.

A pharmaceutically composition containing an aromatase inhibitor and/or an EGFR antagonist or inhibitor can be prepared according to well known techniques to those skilled in the art. For instance a pharmaceutical

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composition containing exemestane can be prepared according to US 4,808,616.

CLAIMS

1. Use of an aromatase inhibitor in the manufacture of a pharmaceutical composition for the treatment of a hormone-dependent disorder characterized by the overexpression of EGFR, wherein the pharmaceutical composition is for administration in combination therapy with a composition comprising an EGFR antagonist or an EGFR inhibitor, in amounts effective to produce a superadditive or synergistic effect.
2. Use, according to claim 1, wherein the disorder is breast, cervical, ovarian or endometrial cancer.
3. Use, according to claim 2, wherein the disorder is breast cancer.
4. Use, according to any one of the preceding claims, wherein the aromatase inhibitor is selected from exemestane, aminoglutethimide, roglethimide, pyridoglutethimide, anastrozole, trilostane, testolactone, formestane, atamestane, 1-methyl-1,4-androstadiene-3,17-dione (MAD), ketokonazole, fadrozole, letrozole, vorozole and anastrozole.
5. Use, according to claim 4, wherein the aromatase inhibitor is exemestane.
6. Use, according to any one of the preceding claims, wherein the EGFR inhibitor is an antibody against EGFR.
7. Use, according to claim 6, wherein the antibody is selected from chimerized antibody C225 and human antibodies E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 and E7.6.3.

8. Use according to claim 6, wherein the antibody is selected from chimerized antibody C225 and human antibody E7.6.3.
- 5
9. Use, according to any one of claims 1 to 5, wherein the EGFR antagonist is selected from ZM 105180, CP-358774 and ZD 1839.
- 10 10. A product comprising an aromatase inhibitor and an EGFR antagonist or EGFR inhibitor, as a combined preparation for simultaneous, separate or sequential administration, in amounts effective to produce a synergistic or superadditive therapeutic effect, in the
- 15 treatment of a hormone-dependent disorder characterized by the overexpression of EGFR.
11. A method of treating a human being suffering from a hormone-dependent disorder characterized by the
- 20 overexpression of EGFR, said method comprising administering to said human being, simultaneously, separately or sequentially, an aromatase inhibitor and an EGFR antagonist or EGFR inhibitor, in amounts effective to produce a superadditive or synergistic
- 25 therapeutic effect.
12. A method for reducing the side effects caused by the treatment of a human being suffering from a hormone-dependent tumor overexpressing EGFR, with an aromatase
- 30 inhibitor, the method comprising administering to said human being a combined preparation comprising an aromatase inhibitor and an EGFR antagonist or an EGFR inhibitor, in amounts effective to produce a superadditive or synergistic antitumor effect, while
- 35 controlling the growth of neoplasm formation.

13. A method for reducing the side effects caused by the treatment of a human being suffering from a hormone-dependent tumor overexpressing EGFR with an EGFR antagonist or EGFR inhibitor, the method comprising administering to said human being a combined preparation comprising an EGFR antagonist or an EGFR inhibitor and an aromatase inhibitor, in amounts effective to produce a superadditive or synergistic antitumor effect, while controlling the growth of neoplasm formation.

14. A method according to any one of claims 11, 12 or 13 wherein the aromatase inhibitor and the EGFR antagonist or EGFR inhibitor are administered in a sequential, separate or a substantially simultaneous manner.

2020
Bogotá, D.C.,

Doctora:
Luz Clemencia de Páez
Apoderada

Oficio N°: 213803

ASUNTO:	Radicación PCT N°	08-82662
	Trámite	011
	Evento	378
	Actuación	440
	Folios	009

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Cielo Ángela Peña Rodríguez, en su calidad de apoderada de Procaps S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


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

El anterior oficio fue notificado por fijación en lista de fecha, 22 OCT. 2010.

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