

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

Numero del expediente: 08-067.099

Solicitante: **WORLD-TRADE IMPORT-EXPORT WTIE, A.G**

**SOLICITUD
PUBLICADA**

Apoderado: **DILIA MARIA RODRIGUEZ D' ALEMAN**

Título de la nueva creación o denominación del signo: **COMPOSICIONES FARMACÉUTICAS**

QUE COMPRENDEN SUSTANCIAS INHIBIDORAS DE LAS LIPASAS INTESTINALES COMBINADAS CON UN COMPLEJO O COORDINADO DE DINICOTINATO DE CROMO PARA SU USO EN EL TRATAMIENTO Y CONTROL DE LA OBESIDAD O SOBREPESO.

Gaceta: 606

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: PROCAPS S.A. Dirección: CALLE 80 No. 78b-201 Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BARRANQUILLA	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Número <u>890.106.527-5</u>
	Teléfono: 371 99 00 Fax: 373 08 18 E-mail: _____	
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 <u>51.940.252</u> TP <u>82701</u>

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. _____

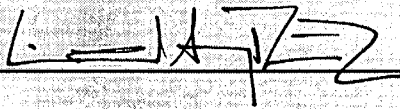
Fecha _____

⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo 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



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 08 67099

Asunto : Oposición a la solicitud de patente de Invención titulada
"COMPOSICIONES FARMACÉUTICAS QUE
COMPRENDEN SUSTANCIAS INHIBIDORAS DE LAS
LIPASAS INTESTINALES COMBINADAS CON UN
COMPLEJO O COORDINADO DE DINICOTINATO DE
CROMO PARA SU USO EN EL TRATAMIENTO Y
CONTROL DE LA OBESIDAD O SOBREPESO"

Solicitante : WORLD-TRADE IMPORT-EXPORT, WTIE, AG

Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 606 del 31 de julio de 2009

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 "COMPOSICIONES FARMACÉUTICAS QUE

COMPRENDEN SUSTANCIAS INHIBIDORAS DE LAS LIPASAS INTESTINALES COMBINADAS CON UN COMPLEJO O COORDINADO DE DINICOTINATO DE CROMO PARA SU USO EN EL TRATAMIENTO Y CONTROL DE LA OBESIDAD O SOBREPESO", cuyo titular es WORLD-TRADE IMPORT-EXPORT, WTIE, AG, 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 DINICOTINATO. 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 1 de julio de 2008 reivindicando prioridad bajo la solicitud MX2005PA14090 del 2005-12-20; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 605 del 30 de

junio de 2009, cuya publicación internacional corresponde a la WO2007073134 del 2007-06-28.

2.2. La solicitud colombiana 08 67099 objeto de la presente oposición, se refiere a una composición farmacéutica sinérgica que comprende una combinación sinérgica de un inhibidor de la lipasa intestinal y un complejo O-coordinado de dinicotinato de cromo para el tratamiento de la obesidad y el sobrepeso; donde la combinación sinérgica, en la cual el inhibidor de la lipasa intestinal es el Orlistat y/o cualquiera de sus sales y un complejo O-coordinado de dinicotinato de cromo conocido como dinicotinato de cromo y/o cualquiera de sus sales.

2.3. En primera instancia, se debe advertir que algunas reivindicaciones también se refieren a un método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)”*, los usos no están contemplados como patentables; y, Artículo 20.- *“No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso y a un método de tratamiento no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN 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 afecta la patentabilidad de la presente solicitud:



- D1: WO2004078113 publicada el 16 de septiembre de 2004.
- D2: US6159466 publicada el 12 de diciembre de 2000.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela un método para impedir o tratar la obesidad y complicaciones relacionadas con la obesidad en un sujeto que implica una monoterapia con un inhibidor COX-2 o una terapia de combinación con un inhibidor COX-2 y un agente de pérdida de peso convencional. Según esta anterioridad D1 se definen un método para prevenir o tratar la obesidad y las complicaciones relacionadas con la misma, utilizando una monoterapia con un inhibidor de la ciclooxigenasa 2 (COX-2) o una terapia combinada de un inhibidor de COX-2 con uno o más agentes reductores de peso, donde dichos agentes se seleccionan entre un inhibidor de la lipasa, en concreto orlistat o derivados de cromo, tal como el picolinato de cromo (ver reivindicaciones 2, 8 y 9). Este documento D1, por lo tanto ya revela combinaciones de orlistat con derivados de cromo tal como el picolinato de cromo para el tratamiento de la obesidad.

2.6. Por su parte, el documento D2 revela en el resumen que la invención comprende una composición acuosa para una dieta humana, con compuestos metálicos en formas biológicamente activas como un complemento. Particularmente en la descripción, particularmente a partir de la columna 5, línea 14 y siguientes, composiciones acuosas que comprende un dinicotinato de cromo, usada para preparar un producto de levadura enriquecido por cromo que tiene un alto contenido intracelular de cromo biológicamente atado trivalente en una forma, o formas, que son biológicamente activas y no tóxicas, donde el método para preparar la levadura enriquecida por cromo comprende ponerla en contacto con

células de levadura vivas (*Saccharomyces boulardii* sequela PY31) en una suspensión acuosa del complejo de dinicotinato de cromo glicinato en niveles entre aproximadamente 200 ppm y aproximadamente 20,000 complejo de cromo ppm, y preferentemente aproximadamente 500 ppm a aproximadamente 15,000 ppm. Por lo tanto esta anterioridad D2 ya revela usos del dinicotinato de cromo en preparaciones para dietas corporales en los seres humanos. Por lo tanto, este documento objeto de oposición a la luz del documento D2 carece evidentemente de ALTURA O NIVEL INVENTIVO, dado que cualquier persona versada en la materia puede llegar de manera evidente, combinando la materia revelada aquí en la anterioridad D2 con lo indicado en el documento D1, para llegar a conformar una combinación sinérgica de un inhibidor de la lipasa intestinal tal como orlistat y un complejo O-coordinado de dinicotinato de cromo para el tratamiento de la obesidad y el sobrepeso.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08 67099 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.

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

2.8.1. 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, 20 de diciembre de 2005, cualquier persona versada en la materia puede llegar de manera evidente, combinando la materia revelada aquí en la anterioridad D2

con lo indicado en el documento DL, para llegar a conformar una combinación sinérgica de un inhibidor de la lipasa intestinal tal como orlistat y un complejo O-coordinado de dinicotinato de cromo para el tratamiento de la obesidad y el sobrepeso, sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 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*". La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.9. 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.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada
"COMPOSICIONES FARMACÉUTICAS QUE COMPRENDEN

SUSTANCIAS INHIBIDORAS DE LAS LIPASAS INTESTINALES COMBINADAS CON UN COMPLEJO O COORDINADO DE DINICOTINATO DE CROMO PARA SU USO EN EL TRATAMIENTO Y CONTROL DE LA OBESIDAD O SOBREPESO", cuyo titular es WORLD-TRADE IMPORT-EXPORT, WTIE, AG, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 606 del 31 de julio de 2009.

3. PRUEBAS

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

- D1: WO2004078113 publicada el 16 de septiembre de 2004.
- D2: US6159466 publicada el 12 de diciembre de 2000.

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



Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

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: WO2004078113 publicada el 16 de septiembre de 2004.
- D2: US6159466 publicada el 12 de diciembre de 2000.

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

NII : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 81,19'
FECHA : OCTUBRE 28 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-067099- -00004-0000

Fecha: 2009-10-28 16:47:57 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 204

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	129950225	05/10/2009	1,722,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEMAS COMERCIALES	287,000.00
		TOTAL :	\$ 287,000.00

SON: DOSCIENTOS OCHENTA Y SIETE 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. 08 067.099, titulada "**COMPOSICIONES FARMACÉUTICAS QUE COMPRENDEN SUSTANCIAS INHIBIDORAS DE LAS LIPASAS INTESTINALES COMBINADAS CON UN COMPLEJO O COORDINADO DE DINICOTINATO DE CROMO PARA SU USO EN EL TRATAMIENTO Y CONTROL DE LA OBESIDAD O SOBREPESO**", cuyo titular es **WORLD-TRADE IMPORT-EXPORT, W.T.I.E. AG.**, publicada en la gaceta No. 606 del 31 de julio de 2009.

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 y judicialmente 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 16 días del mes de Octubre de 2009.

PROCAPS S.A.

C.C. No. 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 TERCERA DEL CIRCULO DE BARRANQUILLA
ALFONSO LUIS AVILA FADUL
DILIGENCIA DE PRESENTACION PERSONAL Y
RECONOCIMIENTO

El suscrito Notario certifica que este escrito fue presentado personalmente por:
WALTER FANAKA TATERAWA

Identificado con: 6751915 de PAWURA

Quien declara que su contenido es cierto y que la firma puesta en él es suya.

[Firma]
FIRMA

19 OCT. 2009

NOTARIO TERCERO DE BARRANQUILLA





***** Pag. 1
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
12*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

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.".-----

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

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

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

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

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 razon social, por la denominacion 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:

Numero	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:

PROCAPS S.A.-----

SIGLA: PROCAPS.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.



***** Pag. 2
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
12*****

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

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 cosméticas, para uso y consumo humano y veterinario. c) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas, alimenticias y cosméticas 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 cosméticas, 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, 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, cosméticos y

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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.-----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
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

C E R T I F I C A

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 transacion. 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. 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

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



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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, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la socieda 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 facultades 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 Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junra Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para

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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	CC.*****7,463,982
2. Minski Gontovnik Meyer	CC.*****7,461,324
3. Minski Gontovnik Jose	CC.*****8,671,834

Suplentes

1. Minski Zirberblum Elliot	CC.*****72,219,541
2. Minski Deitel Daniel	*****
3. Minski Sharon	PA.*990,212,082,805

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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 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
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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
Suplente del Revisor Fiscal.
Duarte Diaz David

Identificación

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 Notaria 2 a. 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 Legaql 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

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

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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 día que se realice la respectiva transacción. 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 representación 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 también los demás 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 representación de ----- PROCANPS S.A., suscriban las declaraciones, reportes y cualquier documento relacionado con los trámites 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 ----- representación de PROCAPS S.A.; endosen los títulos 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 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 condición 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 -----

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

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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. fajon

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
16 September 2004 (16.09.2004)

PCT

(10) International Publication Number
WO 2004/078113 A2

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(25) Filing Language: English
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(30) Priority Data:
60/451,885 4 March 2003 (04.03.2003) US

(71) Applicant (for all designated States except US): **PHARMACIA CORPORATION** [US/US]; 700 Chesterfield Parkway West, Chesterfield, Missouri 63017-1732 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BRIGGS, Michael** [US/US]; 71 Spring Street, Shrewsbury, Massachusetts 01545 (US). **ORNBERG, Richard** [US/US]; 26118 Research Road, Hayward, CA 94545 (US). **HAUSER, Scott** [US/US]; 2008 Telford Dr., St. Louis, MO 63125 (US). **KOKI, Alane** [US/GB]; 145 Hillberry Road, Birch Hill, Bracknell RG12 7ZY (GB).

(74) Agent: **NELSON MULLINS RILEY & SCARBOROUGH LLP**; P.O. Box 11070, Columbia, South Carolina 29211-1070 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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

(54) Title: TREATMENT AND PREVENTION OF OBESITY WITH COX-2 INHIBITORS ALONE OR IN COMBINATION WITH WEIGHT-LOSS AGENTS

(57) Abstract: A method for preventing or treating obesity and obesity-related complications in a subject involves a monotherapy with a Cox-2 inhibitor or a combination therapy with a Cox-2 inhibitor and a conventional weight-loss agent. Also described are therapeutic compositions comprising a Cox-2 inhibitor and a conventional weight-loss agent. Pharmaceutical compositions and kits for implementing the present method are also described.



WO 2004/078113 A2

**TREATMENT AND PREVENTION OF OBESITY WITH COX-2
INHIBITORS ALONE OR IN COMBINATION WITH WEIGHT-LOSS
AGENTS**

5

**CROSS REFERENCE TO RELATED PATENTS AND PATENT
APPLICATIONS**

[0001] This application is related to and claims the priority benefit of U.S. Provisional Patent Application Serial No. 60/451,885 filed March 4, 2003, which is incorporated by reference herein in its entirety.

10

BACKGROUND OF THE INVENTION

(1) Field of the Invention:

[0002] The present invention relates to the prevention and treatment of obesity and obesity-related complications, and more particularly to the prevention and treatment obesity and obesity-related complications with a Cox-2 inhibitor alone or in combination with a weight-loss agent.

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(2) Description of the Related Art:

[0003] The incidence of obesity has increased dramatically throughout the world, most notably over the last 2 decades. By the year 2000, a total of 38.8 million American adults or 30% of the population met the classification of obesity, defined as having a body mass index score of 30 kg/m² or more. See Mokdad, A., et al., *JAMA* 286(10):1195-1200 (2001). The deleterious consequences of obesity are considerable. Recent estimates attribute 280,000 deaths a year in the United States to "overnutrition," making it second only to cigarette smoking as a leading cause of death. See *The Merck Manual of Diagnosis & Therapy, Beers & Brakow, 17th edition*, Published by Merck Research Labs, Sec. 1, Chapter 5, *Nutritional Disorders, Obesity* (1999).

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[0004] The accumulation of excess fat is a known risk factor for developing many obesity-related complications including hypertension, dyslipidemia, type 2 diabetes, stroke, gallbladder disease, cardiovascular disease, osteoarthritis, hypercholesterolemia, sleep apnea, respiratory problems, cancer, stroke and many other disorders. With regard to this

wide range of health complications, the need to develop new and effective strategies in controlling obesity and obesity-related complications is becoming increasingly important.

5 [0005] Most attempts to treat obesity to date, except for several types of surgical intervention, have failed to result in a sustained reduction of weight. Moreover, about 90 to 95 percent of persons who lose the weight subsequently regain it. See Rosenbaum, *et al.*, *N. Engl. J. Med.* 337(6):396-407 (1997). Pharmacotherapy treatment principles are limited and have suffered many setbacks in recent years. For example, several
10 obesity drugs have been recalled by the FDA because of incidences of undesirable side effects.

[0006] Currently, the only two FDA-approved anti-obesity drugs are orlistat, a lipase inhibitor, and sibutramine, a serotonin reuptake inhibitor. Orlistat acts by blocking the absorption of fat into the body. An unpleasant
15 side effect with orlistat, however, is the passage of undigested oily fat from the body. Sibutramine is an appetite suppressant that acts by changing the brain levels of serotonin, but in the process, also causes the elevation of blood pressure and an increase in heart rate. Of concern is that both orlistat and sibutramine fail to address the underlying biochemical
20 processes that lead to obesity.

[0007] Other appetite suppressants, such as amphetamine derivatives, are highly addictive and have the potential for abuse. Moreover, different subjects respond differently to weight-loss medications, and some subjects experience more weight loss than others and keep the weight off for longer
25 periods. Thus, current pharmacotherapy treatments are problematic and novel strategies or novel strategies combined with weight-loss agents are needed for the prevention and treatment of obesity and obesity-related disorders.

[0008] In a general sense, obesity results simply from an imbalance in
30 energy intake and utilization. In actuality, however, obesity is a much more complex syndrome stemming from a myriad of both environmental and genetic determinants. Specifically, when the imbalance is a result of

too much energy intake relative to utilization, it ultimately triggers the biochemical process of adipogenesis, which is an increase in size and number of adipocytes (fat cells). Adipogenesis is a two-step developmental process by which an undifferentiated mesenchymal cell differentiates into a pre-adipocyte cell, which then undergoes a secondary differentiation step to become a lipid-filled mature adipocyte.

[0009] The process of pre-adipocyte differentiation is controlled by a cascade of transcription factors, most notably those of the peroxisome proliferator-activated receptor (PPAR) families, which combine to regulate each other and to control the expression of adipocyte-specific genes. One such adipocyte-specific gene, the *obese* (*ob*) gene, was recently identified. See Zhang, Y., *et al.*, *Nature* 372:425-432 (1994). The *ob* gene has been found to encode a hormone released by adipose tissue, referred to as leptin, that plays a major role in the regulation of appetite, energy intake and energy expenditure. See Halaas, J., *et al.*, *Science* 269(5223):543-6 (1995). Injected leptin has been reported to reduce body weight and food intake in mice through appetite suppression and by increasing the rate of metabolism. *Id.*

[00010] PPARs belong to the nuclear receptor superfamily of ligand-activated transcription factors. Once bound by a ligand, PPARs heterodimerize with 9-cis retinoic acid receptors (RXRs) in the nucleus. These heterodimers bind to specific peroxisome-proliferator response elements (PPRE) in the promoter of target genes, thereby regulating transcription and expression of these genes. Three isoforms of PPARs, alpha, delta (also known as beta or Nuc-1), and gamma, have been identified and differ in their tissue distribution, affinity for particular ligands, and physiological consequences. See *e.g.* Corton, J.C., *et al.*, *Annu. Rev. Pharmacol. Toxicol.* 40:491-518 (2000) and Chawla, A., *et al.*, *Science* 294:1866 - 1870 (2001).

[00011] PPAR-gamma is a nuclear hormone receptor expressed predominantly in adipose tissue. Of particular importance, is that ligand-dependant activation of the PPAR-gamma receptor triggers pre-adipocyte

differentiation. See Forman, B., *et al.*, *Cell* 83(5):803-12 (1995). One of the ligands identified as responsible for activation of PPAR-gamma is the naturally occurring prostaglandin, 15-deoxy-delta(12,14)-(15d)-PGJ2 (PGJ2). See Kliewer, S., *et al.*, *Cell* 83(5):813-9 (1995).

5 Cyclooxygenase enzymes (Cox; prostaglandin synthase, EC 1.14.99.1) are responsible for metabolizing arachidonic acid to prostaglandin H₂, which, in turn, serves as a precursor for the biosynthesis of several prostaglandins, including PGJ2. See e.g. Hamberg, *et al.*, *Proc. Natl. Acad. Sci. USA* 70:899-903 (1973) and DuBois, R., *et al.*, *Carcinogenesis* 19(1):49-53 (1998).

10 [00012] Within the adipogenesis pathway, there are many points at which pre-adipocyte differentiation may be successfully interrupted. For example, expression of the PPAR-gamma receptor itself may be downregulated. Also, synthesis of the PPAR-gamma ligand, PGJ2, may be blocked, thus preventing receptor activation. Inhibiting the synthesis of
15 any other transcription factor or receptor related to adipogenesis initiation should have efficacy against obesity and obesity-related disorders. Moreover, obesity has been implicated on at least one occasion as a disorder that arises as a low-grade systemic inflammatory disease. See
20 Das, U., *et al.*, *Nutrition* 17:953-66 (2001). Thus, anti-inflammatory compounds may also slow or inhibit pre-adipocyte differentiation. However, successful treatment of obesity via interruption of the adipogenesis pathway with pharmaceutically acceptable medicaments is currently lacking.

25 [00013] Historically, physicians have treated inflammation-related disorders with a regimen of nonsteroidal anti-inflammatory drugs (NSAIDs), such as, for example, aspirin and ibuprofen. Undesirably, however, some NSAIDs are known to cause gastrointestinal (GI) bleeding or ulcers in patients undergoing consistent long term regimens of NSAID
30 therapy.

[00014] A reduction of unwanted side effects of common NSAIDs was made possible by the discovery that two cyclooxygenases are involved in

the transformation of arachidonic acid as the first step in the prostaglandin synthesis pathway. These enzymes exist in two forms and have been termed cyclooxygenase-1 (Cox-1) and cyclooxygenase-2 (Cox-2). See Needleman, P., *et al.*, *J. Rheumatol.* 24, Suppl.49:6-8 (1997) and Fu, J., *et al.*, *J. Biol. Chem.* 265(28):16737-40 (1990).

[00015] Cox-1 is a constitutive enzyme responsible for the biosynthesis of prostaglandins in the gastric mucosa and in the kidney. Cox-2 is an enzyme that is produced by an inducible gene that is responsible for the biosynthesis of prostaglandins in inflammatory cells. Inflammation causes the induction of Cox-2, leading to the release of prostanoids (prostaglandin E2), which sensitize peripheral nociceptor terminals and produce localized pain hypersensitivity, inflammation, and oedema. See *e.g.* Samad, T. A. *et al.*, *Nature* 410(6827):471-5 (2001). Many common NSAIDs are now known to be inhibitors of both Cox-1 and Cox-2. Accordingly, when administered in sufficiently high levels, these NSAIDs not only alleviate the inflammatory consequences of Cox-2 activity, but also inhibit the beneficial gastric maintenance activities of Cox-1.

[00016] Research into the area of arachidonic acid metabolism has resulted in the discovery of compounds that specifically inhibit the Cox-2 enzyme to a greater extent than the activity of Cox-1. The Cox-2 selective inhibitors are believed to offer advantages that include the capacity to prevent or reduce inflammation while avoiding harmful side effects associated with the inhibition of Cox-1. Thus, Cox-2 selective inhibitors have shown great promise for use in therapies -- especially in therapies that require maintenance administration, such as for pain and inflammation control.

[00017] While the effects of Cox-2 inhibitors on inflammation and inflammation-related disorders have been relatively widely recognized, the effects of Cox-2 inhibitors on obesity have not been as widely reported. In fact, it has been reported in at least one instance that Cox-2 inhibitors may actually interfere with successful suppression of pre-adipocyte differentiation. See Yokota, T., *et al.*, *J. Clin. Invest.* 109(10):1303-10 (2002).

[00018] Despite the recent advances that have been made in understanding the causes for obesity, it remains a largely intractable disorder. It would be useful, therefore, to provide efficacious methods and compositions for the prevention, treatment and amelioration of obesity and obesity-related complications.

SUMMARY OF THE INVENTION

[00019] Briefly, therefore, the present invention is directed to a novel method of preventing and treating obesity and obesity-related complications in a subject comprising administering to the subject a Cox-2 inhibitor.

[00020] The present invention is also directed to a method of preventing and treating obesity and obesity-related complications in a subject comprising administering to the subject a Cox-2 inhibitor and one or more weight-loss agents.

[00021] The present invention is also directed to a novel therapeutic composition comprising at least one Cox-2 inhibitor and one or more weight-loss agents.

[00022] The present invention is also directed to a novel method of modulating adipogenesis in a subject comprising administering to the subject a Cox-2 inhibitor alone or in combination with one or more weight-loss agents.

[00023] The present invention is also directed to a pharmaceutical composition comprising a Cox-2 inhibitor, a weight-loss agent, and a pharmaceutically acceptable carrier.

[00024] The present invention is also directed to a novel kit comprising one dosage form comprising a Cox-2 inhibitor and a second dosage form comprising a weight-loss agent.

[00025] Among the several advantages found to be achieved by the present invention, therefore, may be noted the provision of improved treatment methods and compositions for obesity, the provision of such improved methods and compositions comprising Cox-2 inhibitors alone or in combination with one or more weight-loss agents that are useful for

ameliorating, treating and preventing obesity and obesity-related complications.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

5 [00026] In accordance with the present invention, it has been discovered that obesity and obesity-related complications may be treated, prevented, and ameliorated in a subject by administering to the subject a Cox-2 inhibitor alone or in combination with one or more weight-loss agents.

10 [00027] For purposes of the present invention, the novel monotherapy or combination therapy comprising at least one Cox-2 inhibitor alone or in combination with at least one weight-loss agent is also useful for the purpose of preventing and treating obesity and obesity-related complications in a subject that is in need of such prevention and treatment.

15 [00028] Thus, the monotherapy or combination therapy of the present invention would be useful, for example, to cause weight loss in an overweight or obese subject or in any subject who desires to lose weight, to reduce the death rate or the number of hospitalizations, or to prevent or retard, in subjects, the development of complications associated with being overweight or obese, such as, for example, diabetes, cardiovascular diseases, hypertension, hypercholesteremia, and stroke, which eventually
20 arise from being chronically overweight or obese.

[00029] The administration of a Cox-2 inhibitor for the prevention and treatment of obesity and obesity-related complications is unexpectedly an effective treatment therapy. Such administration is effective for improving the symptoms of obesity and obesity-related complications without the
25 disadvantages of current treatments.

[00030] Furthermore, the administration of a Cox-2 inhibitor in combination with a weight-loss agent for the prevention or treatment of obesity or obesity-related complications is an effective treatment for obesity or obesity-related complications, and in preferred embodiments, is
30 superior to the use of either agent alone. For example, the combination therapy is effective for lowering the dosages of weight-loss agents that are normally prescribed as a monotherapy. The administration of lower

dosages of weight-loss treatment agents provides a reduction in side effects corresponding to such agents. Moreover, in preferred embodiments, the combination therapy demonstrates a synergistic efficacy for treating and preventing obesity and obesity-related complications that is greater than what would be expected from simply combining the two therapies.

5 [00031] As used herein, the term "obesity" is defined as having a high amount of body fat or adipose tissue in relation to lean body mass. Obesity may arise in a subject via several determinants including environmental, physiological, and genetic determinants. See *The Merck*
10 *Manual of Diagnosis & Therapy, Beers & Brakow, 17th edition*, Published by Merck Research Labs, *Sec. 1, Chapter 5, Nutritional Disorders, Obesity* (1999). For the present invention, however, the term "obesity" is meant to include any fat or weight in a subject who desires to lose such weight or
15 fat. Thus, reference to the "treatment or prevention of obesity" encompasses any subject who desires to reduce their body weight or reduce adipose (fat) tissue mass.

[00032] Accordingly, the methods and compositions of the present invention encompass the treatment or prevention of obesity by causing the
20 loss of weight (weight-loss) in a subject who desires or requires weight-loss. The amount of body fat (or adiposity) includes concern for both the distribution of fat throughout the body and the size of the adipose tissue deposits.

[00033] For example, professional athletes may, on occasion, need to
25 lose additional weight even though their weights would have been considered ideal or normal before following the methods of the present invention or taking the compositions taught herein. Therefore, the present invention encompasses a subject who simply desires to lose weight and is not necessarily suffering from obesity or being overweight or suffering from
30 a weight-related disorder. The present invention's methods and compositions encompass such weight-loss in those individuals through the "treatment or prevention of obesity."

[00034] As used herein, the term "overweight" refers to increased body weight in relation to height, when compared to a desirable weight.

However, overweight may or may not be due to increases in body fat. It may also be due to an increase in lean muscle. For example, professional athletes may be very lean and muscular, with very little body fat, yet they may weigh more than others of the same height. While they may qualify as "overweight" due to their large muscle mass, they are not necessarily "overly fat." However, the present invention encompasses methods and compositions that provide weight loss to a subject that desires weight loss regardless of whether they are overly fat, overweight, or obese.

[00035] As used herein, the term "obesity-related complication" refers to any condition where the accumulation of excess fat is a risk factor for developing health complications. Over time, weight loss in obese individuals may reduce a number of health risks. Studies looking at the effects of weight-loss medication treatment on obesity-related health risks have found that some agents lower blood pressure, blood cholesterol, and triglycerides (fats) and decrease insulin resistance (the body's inability to use blood sugar) via a reduction in weight.

[00036] For purposes of the present invention, obesity-related complications include, but are not limited to, hypertension, dyslipidemia, type 2 diabetes, stroke, gallbladder disease, cardiovascular disease, osteoarthritis, rheumatoid arthritis, hypercholesterolemia, stable angina, unstable angina, atherosclerosis, sleep apnea, respiratory problems, cancer, stroke and many other disorders. Thus, the reduction of excess fat by the methods and compositions of the present invention also helps to prevent or to treat any health complication arising from the condition of having the excess fat.

[00037] Accordingly, the methods and compositions of the present invention treat or prevent obesity-related health complications. In animals and model organisms, diet induced weight loss or low caloric diets have provided evidence for increased longevity of the animals. This may be due to either the absence of disease causing life shortening, or actual

extended lifespan. Therefore, the treatments described herein provide a healthier, more productive and longer lifespan for both animals and humans.

5 [00038] The compositions and methods of the present invention also encompass the post surgical maintenance of weight loss, from liposuction or more direct surgical resection of adipose in that adipose differentiation is inhibited and thus, the accumulation of new fat/adipose mass will be reduced allowing for reduced numbers of repeat procedures and complications arising therefrom.

10 [00039] In the present invention, a Cox-2 inhibitor alone or in combination with a weight-loss agent is administered to a subject according to standard routes of drug delivery that are well known to one of ordinary skill in the art. The particular route and dosage of the Cox-2 inhibitor alone or in combination with the weight-loss agent depends upon
15 the needs of the subject being treated, the type of treatment, the efficacy of the compound and the degree of obesity severity in the subject.

[00040] It is preferred that the amount of a Cox-2 inhibitor that is administered to a subject comprises an effective amount of a Cox-2 inhibitor. It is further preferred that the amount of a Cox-2 inhibitor and the
20 amount of a weight-loss agent together comprise an effective amount of the combination of the two treatment agents. Still further preferred is that the amount of the monotherapy with the Cox-2 inhibitor comprises a therapeutically amount of the Cox-2 inhibitor. Further preferred is that the amount of the co-therapy with the Cox-2 inhibitor and weight-loss agent
25 comprise a therapeutically effective amount of the co-therapy.

[00041] As used herein, an "effective amount" means the dose or amount to be administered to a subject and the frequency of administration to the subject, which is readily determined by one having ordinary skill in the art, by the use of known techniques and by observing
30 results obtained under analogous circumstances.

[00042] In determining the effective amount or dose, a number of factors are considered by the attending diagnostician, including, but not limited to,

the potency and duration of action of the compounds used, the nature and severity of the illness to be treated, as well as the sex, age, weight, general health and individual responsiveness of the patient to be treated, and other relevant circumstances.

5 [00043] As used herein, the terms "therapeutically effective" are intended to qualify the amount of an agent for use in therapy which will achieve the goal of preventing, or improvement in the severity of, the disorder being treated, while avoiding adverse side effects typically associated with alternative therapies. An obesity symptom or an obesity-related complication symptom is considered ameliorated or improved if
10 any benefit is achieved, no matter how slight. For example, any reduction in the weight of a subject would be considered an ameliorated symptom. Likewise, any alteration of the normal process of adipogenesis would be considered amelioration of an obesity symptom. Furthermore, any
15 reduction in symptom severity of an obesity-related complication is considered an ameliorated symptom. An obesity-related complication, such as hypertension, is considered ameliorated, if after administration of the compositions and methods of the present invention, a reduction in blood pressure is found.

20 [00044] As used herein, the terms "prophylactically effective" refer to an amount of a Cox-2 inhibitor alone or in combination with a weight-loss agent that causes a decrease in the frequency of incidence of obesity or an obesity-related complication. The term "prophylactic" refers to the prevention of obesity or an obesity-related complication, whereas the term
25 "therapeutic" refers to the effective treatment of an existing disorder such as obesity or an obesity-related complication.

[00045] As used herein, the phrases "combination therapy", "co-administration", "co-administering", "administration with", "administering", "combination", or "co-therapy", when referring to use of a Cox-2 inhibitor in
30 combination with a weight-loss agent, are intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well

to embrace co-administration of these agents in a substantially simultaneous manner. Thus, the Cox-2 inhibitor and weight-loss agent may be administered in one therapeutic dosage form, such as in a single capsule, tablet, or injection, or in two separate therapeutic dosage forms, such as in separate capsules, tablets, or injections.

[00046] Sequential administration of such treatments encompasses both relatively short and relatively long periods between the administration of each of the two drugs of the present method. However, for purposes of the present invention, the second drug is administered while the first drug is still having an efficacious effect on the subject. Thus, the present invention takes advantage of the fact that the simultaneous presence of the combination of a Cox-2 inhibitor and a weight-loss agent in a subject has a greater efficacy than the administration of either agent alone.

[00047] Preferably, the second of the two drugs is to be given to the subject within the therapeutic response time of the first drug to be administered. For example, the present invention encompasses administration of a Cox-2 inhibitor to the subject and the later administration of a weight-loss agent, as long as the weight-loss agent is administered to the subject while the Cox-2 inhibitor is still present in the subject at a level, which in combination with the level of the weight-loss agent is therapeutically effective, and vice versa.

[00048] As used herein, the terms "therapeutic response time" mean the duration of time that a compound is present within a subject's body at therapeutic concentrations.

[00049] As used herein, the term "monotherapy" is intended to embrace administration of a Cox-2 inhibitor to a subject suffering from an obesity or obesity-related complication as a single therapeutic treatment without an additional therapeutic treatment comprising a weight-loss agent. However, the Cox-2 inhibitor may still be administered in multiple dosage forms.

Thus, the Cox-2 inhibitor may be administered in one therapeutic dosage form, such as in a single capsule, tablet, or injection, or in two separate

therapeutic dosage forms, such as in separate capsules, tablets, or injections.

5 [00050] As used herein, the terms "treating" or "to treat," mean to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms. The term "treatment" includes alleviation, elimination of causation of obesity associated with, but not limited to, any of the diseases or disorders described herein.

10 [00051] The present invention is also directed to a novel method of treating or preventing obesity and obesity-related complications in a subject comprising administering to the subject a Cox-2 inhibitor and one or more weight-loss agents

15 [00052] Without being bound by this or any other theory, it is believed that a therapy comprising a Cox-2 inhibitor is efficacious for impairing the process of adipogenesis, thus preventing or treating obesity and thereby an obesity-related complication. Obesity is a known factor or contributor to generalized inflammatory states and proinflammatory cytokines are produced that affect general health and may predispose toward or exacerbate other causes of inflammation in the body. As Cox-2 inhibitors
20 are effective anti-inflammatory agents, the administration of these agents have beneficial effects in the obese population directly from their anti-inflammatory properties.

25 [00053] Moreover, in preferred embodiments, the combination of a Cox-2 inhibitor and a weight-loss agent provide synergistic effects, which reduces the symptoms associated with obesity and obesity-related complications to a greater extent than either one alone. The term "synergistic" refers to the combination of a Cox-2 inhibitor and a weight-loss agent as a combined therapy having an efficacy for the prevention and treatment of obesity that is greater than what would be expected on
30 the basis of their individual effects

[00054] The synergistic effects of preferred embodiments of the present invention's combination therapy encompass additional unexpected

advantages for the treatment and prevention of obesity. Such additional advantages include, but are not limited to, lowering the required dose of weight-loss agents, reducing the side-effects of weight-loss agents, and rendering those agents more tolerable to subjects in need of obesity therapy.

[00056] Also, the monotherapy and combination therapy of the present invention provide for the treatment of obesity-related complications, which arise indirectly from being obese, by treating the underlying obesity itself. For example, if an obese subject is suffering from obesity-related complications, such as diabetes and hypertension, the treatment of the underlying obesity by the methods and compositions of the present invention will likewise improve the symptoms of the associated complications.

[00057] In one embodiment, the present invention provides a method of preventing obesity and obesity-related complications in a subject comprising administering to the subject a Cox-2 inhibitor alone or in combination with a weight-loss agent.

[00058] As used herein, the terms "to prevent", "preventing", or "prevention" refer to any reduction, no matter how slight, of a subject's predisposition or risk for developing obesity and/or an obesity-related complication. For purposes of prevention, the subject is any subject, and preferably is a subject that is at risk for, or is predisposed to, developing obesity and/or an obesity-related complication.

[00059] As used herein, a subject that is "predisposed to developing obesity and/or an obesity-related complication" or "at risk for developing obesity and/or an obesity-related complication," both of which are used interchangeably herein, includes any subject with an increased chance for developing obesity and/or an obesity-related complication. The subject may be at risk due to genetic predisposition, diet, sedentary lifestyle, age, exposure to obesity-causing agents, and the like. The subject may be at risk due to physiological factors such as anatomical and biochemical abnormalities and certain hormonal diseases or disorders. For example,

the subject may be at risk due to such physiological factors as excessively high levels of oncogenes. The subject may also be at risk for re-developing obesity during a relapse of such a disorder.

5 [00035] In one embodiment, the present invention provides a method of treating obesity and obesity-related complications in a subject comprising administering to the subject a Cox-2 inhibitor alone or in combination with a weight-loss agent.

10 [00036] As used herein, the terms "treating", "treatment", "treated", or "to treat" mean to alleviate obesity symptoms, eliminate the causation either on a temporary or permanent basis, or to alter or slow the appearance of obesity symptoms or symptom worsening. The term "treatment" includes alleviation or elimination of the causation of obesity, including any of the obesity-related complications described herein.

15 [00037] A component of the present invention is a Cox-2 inhibitor. [00038] Inhibitors of the cyclooxygenase pathway in the metabolism of arachidonic acid may inhibit enzyme activity through a variety of mechanisms. By way of example, the Cox-2 inhibitors used in the methods described herein may block the enzyme activity directly by binding at the substrate site of the enzyme. In preferred embodiments, the use of a Cox-2 selective inhibitor is highly advantageous in that it
20 minimizes the gastric side effects that can occur with non-selective non-steroidal anti-inflammatory drugs (NSAIDs), especially where prolonged treatment is expected.

25 [00039] The term "cyclooxygenase-2 inhibitor", or "Cox-2 inhibitor", which can be used interchangeably herein, embrace compounds, which inhibit the Cox-2 enzyme regardless of the degree of inhibition of the Cox-1 enzyme, and include the pharmaceutically acceptable salts of those compounds. For the purposes of the present invention, a compound is considered a Cox-2 inhibitor irrespective of whether the compound inhibits the Cox-2 enzyme to a greater, or lesser degree than the Cox-1 enzyme.

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[0006] The selectivity of a Cox-2 inhibitor varies depending upon the method used for the test is performed and on the inhibitors being tested. However, for the purposes of this specification, the selectivity of a Cox-2 inhibitor can be measured as a ratio of the *in vitro* or *in vivo* IC₅₀ value for inhibition of Cox-1, divided by the IC₅₀ value for inhibition of Cox-2 (Cox-1 IC₅₀/Cox-2 IC₅₀). A Cox-2 selective inhibitor is an inhibitor in which the ratio of Cox-1 IC₅₀ to Cox-2 IC₅₀ is greater than 1. In preferred embodiments, this ratio is greater than 2, more preferably greater than 3, yet more preferably greater than 10, still more preferably greater than 50, and most preferably still greater than 100.

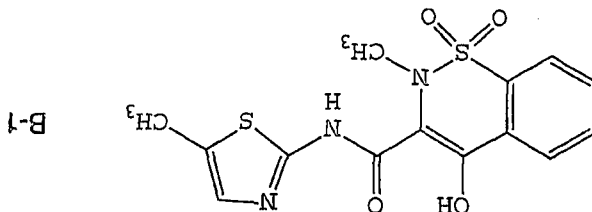
[0007] As used herein, the term "IC₅₀" refers to the concentration of a compound that is required to produce 50% inhibition of cyclooxygenase activity. Preferred Cox-2 selective inhibitors of the present invention have a Cox-2 IC₅₀ of less than about 1 μM, more preferred or less than about 0.5 μM, and even more preferred or less than about 0.2 μM.

[0008] Preferred Cox-2 selective inhibitors have a Cox-1 IC₅₀ of greater than about 1 μM, and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common life-threatening side effects.

[0009] Also included within the scope of the present invention are compounds that are analogs of Cox-2 selective inhibitors. As used herein to refer to Cox-2 selective inhibitors, the term "prodrug" refers to a compound that can be converted into an active Cox-2 selective inhibitor by metabolic or simple chemical processes within the body of the subject. One example of a prodrug for a Cox-2 selective inhibitor is valdecoxib, which is a therapeutically effective prodrug of the tripartite Cox-2 selective inhibitor valdecoxib. An example of a preferred Cox-2 selective inhibitor prodrug is acetylsalicylic acid. A class of prodrugs of Cox-2 selective inhibitors is described in U.S. Patent No. 5,932,598.

[0010] The Cox-2 selective inhibitor of the present invention can be, for example, the Cox-2 selective inhibitor ibuprofen (Formula B-1) (CAS

registry number 71125-38-7), or a pharmaceutically acceptable salt or prodrug thereof.



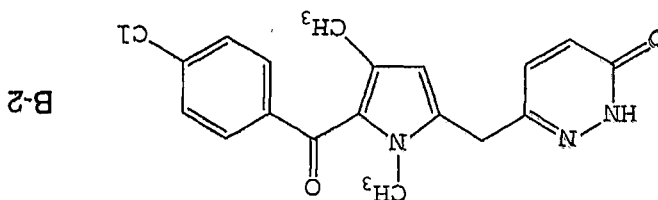
[00073] In another embodiment of the invention the Cox-2 selective

inhibitor can be the Cox-2 selective inhibitor RS 57067, 6-[[5-(4-

chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

Formula B-2 (CAS registry number 179382-91-3), or a pharmaceutically

acceptable salt or prodrug thereof.



[00074] The meaning of any substituent at any one occurrence in Formula I, or any other general chemical formula herein, is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

[00075] The term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylsulfonyl"; it embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl"

radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atoms. The number of

carbon atoms can also be expressed as "C₁-C₅", for example. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, octyl and the like. The term

37

"alkenyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains at least one double bond. Unless otherwise noted, such radicals preferably contain from 2 to about 6 carbon atoms, preferably from 2 to about 4 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkenyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkenyl radicals include propenyl, 2-chloropropenyl, buten-1-yl, isobutenyl, penten-1-yl, 2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, 3-hydroxyhexen-1-yl, hepten-1-yl, octen-1-yl, and the like. The term

10 "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains one or more triple bonds, such radicals preferably containing 2 to about 6 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkynyl radicals may be optionally substituted with groups as described below. Examples of suitable alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals, and the like.

15 [00076] The term "oxo" means a single double-bonded oxygen.

[00077] The terms "hydrido", "-H", or "hydrogen", denote a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical, or two hydrido radicals may be attached to a carbon atom to form a methylene ($-\text{CH}_2-$) radical.

20 [00078] The term "halo" means halogens such as fluorine, chlorine, and bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl, and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have a bromo, chloro, or a fluoro atom within the radical. Dihaloradicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals.

30 Likewise, the term "halo", when it is appended to alkenyl, alkynyl, alkoxy,

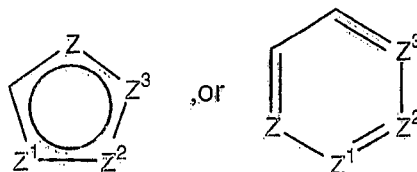
aryl, cycloalkyl, heteroalkyl, heteroaryl, and the like, includes radicals having mono-, di-, or tri-, halo substitution on one or more of the atoms of the radical.

5 [00079] The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals.

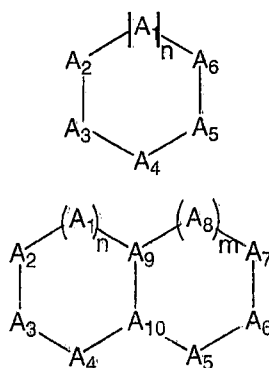
10 [00080] The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of "alkoxy" radicals
15 include methoxy, butoxy, and trifluoromethoxy. Terms such as "alkoxy(halo)alkyl", indicate a molecule having a terminal alkoxy that is bound to an alkyl, which is bonded to the parent molecule, while the alkyl also has a substituent halo group in a non-terminal location. In other words, both the alkoxy and the halo group are substituents of the alkyl
20 chain.

[00081] The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two, or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl,
25 tetrahydronaphthyl, indane, and biphenyl.

[00082] The term "heterocyclyl" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms is replaced by N, S, P, or O. This includes, for example, structures such as:



where Z, Z¹, Z², or Z³ is C, S, P, O, or N, with the proviso that one of Z, Z¹, Z², or Z³ is other than carbon, but is not O or S when attached to another Z atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z, Z¹, Z², or Z³ only when each is C. The term "heterocycle" also includes fully saturated ring structures, such as piperazinyl, dioxanyl, tetrahydrofuranyl, oxiranyl, aziridinyl, morpholinyl, pyrrolidinyl, piperidinyl, thiazolidinyl, and others. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include thienyl, pyrrolyl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, pyranyl, and tetrazolyl. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. The terms aryl or heteroaryl, as appropriate, include the following structures:



where:

when n=1, m=1 and A₁-A₈ are each CR^x or N, A₉ and A₁₀ are carbon;

when n=0, or 1, and m=0, or 1, one of A₂-A₄ and/or A₅-A₇ is optionally S, O, or NR^x, and other ring members are CR^x or N, with the

proviso that oxygen cannot be adjacent to sulfur in a ring. A₉ and A₁₀ are carbon;

when n is greater than or equal to 0, and m is greater than or equal to 0, 1 or more sets of 2 or more adjacent atoms A₁-A₁₀ are sp³ O, S, NR^x, CR^xR^y, or C=(O or S), with the proviso that oxygen and sulfur cannot be adjacent. The remaining A₁-A₈ are CR^x or N, and A₉ and A₁₀ are carbon;

when n is greater than or equal to 0, and m greater than or equal to 0, atoms separated by 2 atoms (i.e., A₁ and A₄) are sp³ O, S, NR^x, CR^xR^y, and remaining A₁-A₈ are independently CR^x or N, and A₉ and A₁₀ are carbon.

[00083] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-\text{SO}_2-$.

"Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. The term "arylsulfonyl" embraces sulfonyl radicals substituted with an aryl radical. The terms "sulfamyl" or "sulfonamidyl", whether alone or used with terms such as "N-alkylsulfamyl", "N-arylsulfamyl", "N,N-dialkylsulfamyl" and "N-alkyl-N-arylsulfamyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-\text{SO}_2-\text{NH}_2$), which may also be termed an "aminosulfonyl". The terms "N-alkylsulfamyl" and "N,N-dialkylsulfamyl" denote sulfamyl radicals substituted, respectively, with one alkyl radical, a cycloalkyl ring, or two alkyl radicals. The terms "N-arylsulfamyl" and "N-alkyl-N-arylsulfamyl" denote sulfamyl radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical.

[00084] The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-\text{CO}_2-\text{H}$. The term "carboxyalkyl" embraces radicals having a carboxyl radical as defined above, attached to an alkyl radical. The term "carbonyl", whether used alone or with other terms, such as "alkylcarbonyl", denotes $-(\text{C}=\text{O})-$.

The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. An example of an "alkylcarbonyl" radical is $\text{CH}_3 - (\text{CO}) -$. The term "alkylcarbonylalkyl" denotes an alkyl radical

substituted with an "alkylcarbonyl" radical. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl (C=O) radical. Examples of such "alkoxycarbonyl" radicals include $(\text{CH}_3)_3\text{C}-\text{O}-\text{C}(=\text{O})-$ and $-(\text{O}=\text{C})-\text{OCH}_3$.

The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. Examples of such "alkoxycarbonylalkyl" radicals include $(\text{CH}_3)_3\text{C}-\text{OC}(=\text{O})-(\text{CH}_2)_2-$ and $-(\text{CH}_2)_2(-\text{O})\text{COCH}_3$. The terms "amido", or "carbonyl", when used alone

or with other terms such as "amidoalkyl", "N-monoalkylamido", "N-monoarylamido", "N,N-dialkylamido", "N-alkyl-N-arylamido", "N-alkyl-N-hydroxyamido" and "N-alkyl-N-hydroxyamidoalkyl", embraces a carbonyl radical substituted with an amino radical. The terms "N-alkylamido" and "N,N-dialkylamido" denote amido groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The terms "N-

monoarylamido" and "N-alkyl-N-arylamido" denote amido radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The term "N-alkyl-N-hydroxyamido" embraces amido radicals substituted with a hydroxyl radical and with an alkyl radical. The term "N-alkyl-N-hydroxyamidoalkyl" embraces alkyl radicals substituted with an N-alkyl-N-hydroxyamido radical. The term "amidoalkyl" embraces alkyl radicals substituted with amido radicals. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with an alkyl radical. The term "amidino" denotes an $-\text{C}(-\text{NH})-\text{NH}_2$ radical. The term "cyanoamidino" denotes an $-\text{C}(-\text{N}-\text{CN})-\text{NH}_2$ radical. The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals such as pyridylmethyl and thienylmethyl.

[00085] The terms "aralkyl", or "arylalkyl" embrace aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenethyl, and diphenethyl. The terms benzyl and phenylmethyl are interchangeable. The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

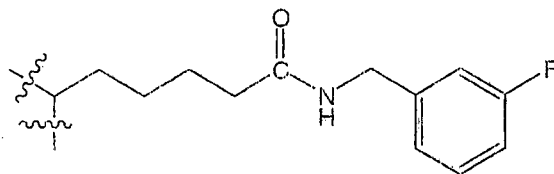
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The term "cycloalkenyl" embraces unsaturated radicals having three to ten carbon atoms, such as cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and cycloheptenyl.

[00086] The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkylthio" is methylthio, (CH₃-S-). The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(-O)- atom. The terms "N-alkylamino" and "N, N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively.

[00087] The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from an organic acid. The term "acylamino" embraces an amino radical substituted with an acyl group. An examples of an "acylamino" radical is acetylamino (CH₃-C(=O)-NH-).

[00088] In the naming of substituent groups for general chemical structures, the naming of the chemical components of the group is typically from the terminal group-toward the parent compound unless otherwise noted, as discussed below. In other words, the outermost chemical structure is named first, followed by the next structure in line, followed by the next, etc. until the structure that is connected to the parent structure is named. For example, a substituent group having a structure such as:



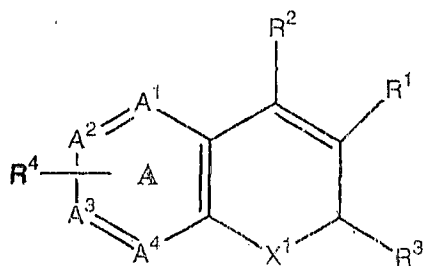
may be referred to generally as a "haloarylalkylaminocarboxylalkyl". An example of one such group would be fluorophenylmethylcarbonylpentyl.

The bonds having wavy lines through them represent the parent structure to which the alkyl is attached.

[00089] Substituent groups may also be named by reference to one or more "R" groups. The structure shown above would be included in a description, such as, "-C₁-C₆-alkyl-COR^u", where R^u is defined to include -NH-C₁-C₄-alkylaryl-R^v, and where R^v is defined to include halo. In this scheme, atoms having an "R" group are shown with the "R" group being the terminal group (*i.e.*, furthest from the parent). In a term such as "C(R^x)₂", it should be understood that the two R^x groups can be the same, or they can be different if R^x is defined as having more than one possible identity.

[00090] In one embodiment of the present invention, the Cox-2 selective inhibitor is of the chromene/chroman structural class, which encompasses substituted benzopyrans or substituted benzopyran analogs, as well as substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the structure of any one of the general Formulas I, II, III, IV, V, and VI, shown below, and including, by way of non-limiting example, the structures disclosed in Table 1, and the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

[00091] Benzopyrans that can serve as a Cox-2 selective inhibitor of the present invention include substituted benzopyran derivatives that are described in U.S. Patent Nos. 6,271,253 and 6,492,390. One such class of compounds is defined by the general formula shown below in formula I:



wherein X¹ is selected from O, S, CR^cR^b and NR^a;

wherein R^a is selected from hydrido, C_1-C_3 -alkyl, (optionally substituted phenyl)- C_1-C_3 -alkyl, acyl and carboxy- C_1-C_6 -alkyl;

wherein each of R^b and R^c is independently selected from hydrido, C_1-C_3 -alkyl, phenyl- C_1-C_3 -alkyl, C_1-C_3 -perfluoroalkyl, chloro, C_1-C_6 -alkylthio, C_1-C_6 -alkoxy, nitro, cyano and cyano- C_1-C_3 -alkyl; or wherein

5 CR^bR^c forms a 3-6 membered cycloalkyl ring;

wherein R^1 is selected from carboxyl, aminocarbonyl, C_1-C_6 -alkylsulfonylaminocarbonyl and C_1-C_6 -alkoxycarbonyl;

wherein R^2 is selected from hydrido, phenyl, thienyl, C_1-C_6 -alkyl and C_2

10 $-C_6$ -alkenyl;

wherein R^3 is selected from C_1-C_3 -perfluoroalkyl, chloro, C_1-C_6 -alkylthio, C_1-C_6 -alkoxy, nitro, cyano and cyano- C_1-C_3 -alkyl;

wherein R^4 is one or more radicals independently selected from hydrido,

15 halo, C_1-C_6 -alkyl, C_2-C_6 -alkenyl, C_2-C_6 -alkynyl, halo- C_2-C_6 -alkynyl, aryl- C_1-C_3 -alkyl, aryl- C_2-C_6 -alkynyl, aryl- C_2-C_6 -alkenyl, C_1-C_6 -alkoxy, methylenedioxy, C_1-C_6 -alkylthio, C_1-C_6 -alkylsulfinyl, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1-C_6 -alkoxy- C_1-C_6 -alkyl,

20 aryl- C_1-C_6 -alkyloxy, heteroaryl- C_1-C_6 -alkyloxy, aryl- C_1-C_6 -alkoxy- C_1-C_6 -alkyl, C_1-C_6 -haloalkyl, C_1-C_6 -haloalkoxy, C_1-C_6 -haloalkylthio, C_1-C_6 -haloalkylsulfinyl, C_1-C_6 -haloalkylsulfonyl, C_1-C_3 -(haloalkyl)- C_3 -hydroxyalkyl, C_1-C_6 -hydroxyalkyl, hydroxyimino- C_1-C_6 -alkyl, C_1-C_6 -alkylamino, arylamino, aryl- C_1-C_6 -alkylamino, heteroarylamino, heteroaryl- C_1-C_6 -alkylamino, nitro, cyano, amino, aminosulfonyl, C_1-C_6 -alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl- C_1-C_6 -alkylaminosulfonyl, heteroaryl- C_1-C_6 -alkylaminosulfonyl,

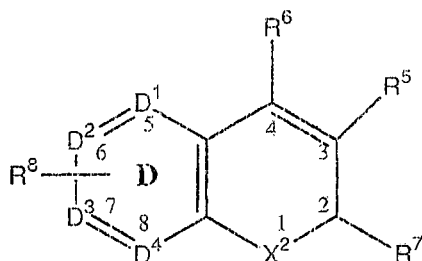
25 heterocyclisulfonyl, C_1-C_6 -alkylsulfonyl, aryl- C_1-C_6 -alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl- C_1-C_6 -alkylcarbonyl, heteroaryl- C_1-C_6 -alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C_1-C_1 -alkoxycarbonyl, formyl, C_1-C_6 -haloalkylcarbonyl and C_1-C_6 -alkylcarbonyl; and

30

wherein the A ring atoms A¹, A², A³ and A⁴ are independently selected from carbon and nitrogen with the proviso that at least two of A¹, A², A³ and A⁴ are carbon;

or wherein R⁴ together with ring A forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinoliziny, quinoxaliny and dibenzofuryl; or an isomer or pharmaceutically acceptable salt thereof.

[00092] Another class of benzopyran derivatives that can serve as the Cox-2 selective inhibitor of the present invention includes compounds having the structure of formula II:



II

wherein X² is selected from O, S, CR^cR^b and NR^a;

wherein R^a is selected from hydrido, C₁-C₃-alkyl, (optionally substituted phenyl)-C₁-C₃-alkyl, alkylsulfonyl, phenylsulfonyl, benzylsulfonyl, acyl and carboxy-C₁-C₆-alkyl;

wherein each of R^b and R^c is independently selected from hydrido, C₁-C₆-alkyl, phenyl-C₁-C₃-alkyl, C₁-C₃-perfluoroalkyl, chloro, C₁-C₆-alkylthio, C₁-C₆-alkoxy, nitro, cyano and cyano-C₁-C₃-alkyl;

or wherein CR^cR^b form a cyclopropyl ring;

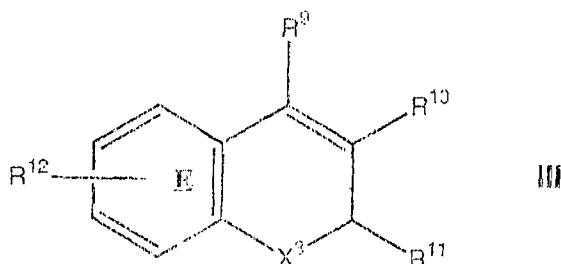
wherein R⁵ is selected from carboxyl, aminocarbonyl, C₁-C₆-alkylsulfonylaminocarbonyl and C₁-C₆-alkoxycarbonyl;

wherein R⁶ is selected from hydrido, phenyl, thienyl, C₂-C₆-alkynyl and C₂-C₆-alkenyl;

wherein R⁷ is selected from C₁-C₃-perfluoroalkyl, chloro, C₁-C₆-alkylthio, C₁-C₆-alkoxy, nitro, cyano and cyano-C₁-C₃-alkyl;

wherein R⁸ is one or more radicals independently selected from hydrido, halo, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, halo-C₂-C₆-

alkynyl, aryl-C₁-C₃-alkyl, aryl-C₂-C₆-alkynyl, aryl-C₂-C₆-alkenyl, C₁-C₆-alkoxy, methylenedioxy, C₁-C₆-alkylthio, C₁-C₆-alkylsulfinyl, =
 O(CF₂)₂O-, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C₁-C₆-alkoxy-
 C₁-C₆-alkyl, aryl-C₁-C₆-alkyloxy, heteroaryl-C₁-C₆-alkyloxy, aryl-C₁-
 5 C₆-alkoxy-C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-haloalkoxy, C₁-C₆-
 haloalkylthio, C₁-C₆-haloalkylsulfinyl, C₁-C₆-haloalkylsulfonyl, C₁-C₃-
 (haloalkyl-C₁-C₃-hydroxyalkyl), C₁-C₆-hydroxyalkyl, hydroxyimino-C₁-
 C₆-alkyl, C₁-C₆-alkylamino, arylamino, aryl-C₁-C₆-alkylamino,
 heteroarylamino, heteroaryl-C₁-C₆-alkylamino, nitro, cyano, amino,
 10 aminosulfonyl, C₁-C₆-alkylaminosulfonyl, arylaminosulfonyl,
 heteroarylaminosulfonyl, aryl-C₁-C₆-alkylaminosulfonyl, heteroaryl-C₁-
 C₆-alkylaminosulfonyl, heterocyclylsulfonyl, C₁-C₆-alkylsulfonyl, aryl-C₁-
 C₆-alkylsulfonyl, optionally substituted aryl, optionally substituted
 heteroaryl, aryl-C₁-C₆-alkylcarbonyl, heteroaryl-C₁-C₆-alkylcarbonyl,
 15 heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C₁-C₆-alkoxycarbonyl,
 formyl, C₁-C₆-haloalkylcarbonyl and C₁-C₆-alkylcarbonyl; and
 wherein the D ring atoms D¹, D², D³ and D⁴ are independently selected
 from carbon and nitrogen with the proviso that at least two of D¹, D², D³
 and D⁴ are carbon; or
 20 wherein R⁸ together with ring D forms a radical selected from naphthyl,
 quinolyl, isoquinolyl, quinoliziny, quinoxaliny and dibenzofuryl;
 or an isomer or pharmaceutically acceptable salt thereof.
 [00093] Other benzopyran Cox-2 selective inhibitors useful in the
 practice of the present invention are described in U.S. Patent Nos.
 25 6,034,256 and 6,077,850. The general formula for these compounds is
 shown in formula III:



wherein X^3 is selected from the group consisting of O or S or NR^a ;

wherein R^a is alkyl;

wherein R^9 is selected from the group consisting of H and aryl;

5 wherein R^{10} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxy carbonyl;

wherein R^{11} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

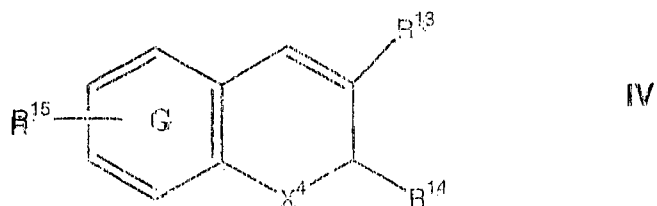
10 wherein R^{12} is selected from the group consisting of one or more radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroaryl amino, heteroarylalkyl amino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl,

15 heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or

20 wherein R^{12} together with ring E forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof; and

including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

[00094] A related class of compounds useful as Cox-2 selective inhibitors in the present invention is described by Formulas IV and V
25 below:



wherein X^4 is selected from O or S or NR^a ;

wherein R^a is alkyl;

wherein R^{13} is selected from carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

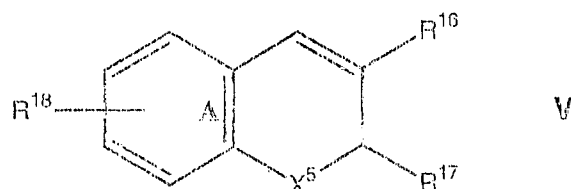
wherein R^{14} is selected from haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R^{15} is one or more radicals selected from hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroaryl amino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

or wherein R^{15} together with ring G forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00095] Formula V is:



wherein:

X^5 is selected from the group consisting of O or S or NR^b ;

R^b is alkyl;

R^{16} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^{17} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and R^{18} is one or more radicals selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylmino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00096] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl; and

R^{18} is one or more radicals selected from the group of consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered nitrogen-containing

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heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl,
lower aralkylcarbonyl, and lower alkylcarbonyl; or
wherein R^{18} together with ring A forms a naphthyl radical;
or an isomer or pharmaceutically acceptable salt thereof.

5 [00097] The Cox-2 selective inhibitor may also be a compound of
Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is carboxyl;

R^{17} is lower haloalkyl; and

10 R^{18} is one or more radicals selected from the group consisting of hydride,
halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino,
amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered
heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl,
lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-
15 containing heterocyclosulfonyl, optionally substituted phenyl, lower
aralkylcarbonyl, and lower alkylcarbonyl; or wherein R^{18} together with ring
A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

20 [00098] The Cox-2 selective inhibitor may also be a compound of
Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower
aralkyl and lower alkoxy carbonyl;

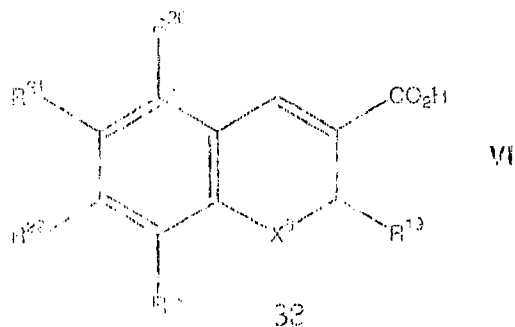
25 R^{17} is selected from the group consisting of fluoromethyl, chloromethyl,
dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl,
difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl,
and trifluoromethyl; and

30 R^{18} is one or more radicals selected from the group consisting of hydride,
chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl,
isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropoxy, *tert*butyloxy,
trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-
dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-

phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or
 5 wherein R² together with ring A forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof.

[00029] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:
 10 X⁵ is selected from the group consisting of oxygen and sulfur;
 R¹⁶ is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxy carbonyl;
 R¹⁷ is selected from the group consisting of trifluoromethyl and pentafluoroethyl; and
 15 R¹⁸ is one or more radicals selected from the group consisting of hydride, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl; or wherein R¹⁸ together with ring A forms a naphthyl radical;
 20 or an isomer or prodrug thereof.

[00030] The Cox-2 selective inhibitor of the present invention can also be a compound having the structure of Formula VI:



wherein:

X^6 is selected from the group consisting of O and S;

R^{19} is lower haloalkyl;

5 R^{20} is selected from the group consisting of hydrido, and halo;

R^{21} is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, and 6-membered nitrogen-containing heterocyclosulfonyl;

10 R^{22} is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

15 R^{23} is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl; or an isomer or prodrug thereof.

[000161] The Cox-2 selective inhibitor can also be a compound of having the structure of Formula VI, wherein:

X^6 is selected from the group consisting of O and S;

20 R^{19} is selected from the group consisting of trifluoromethyl and pentafluoroethyl;

R^{20} is selected from the group consisting of hydrido, chloro, and fluoro;

R^{21} is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, difluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenethylaminosulfonyl,

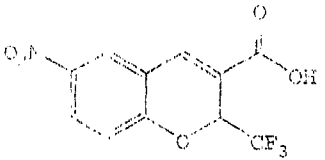
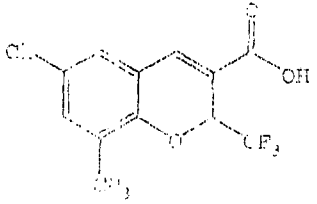
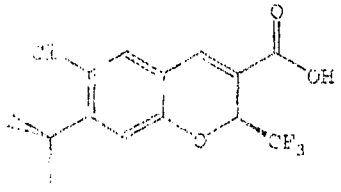
25 methoxypylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl;

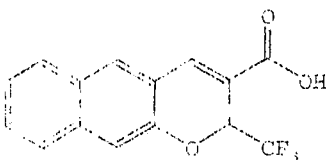
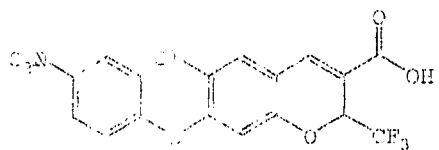
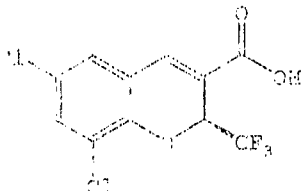
R^{22} is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and

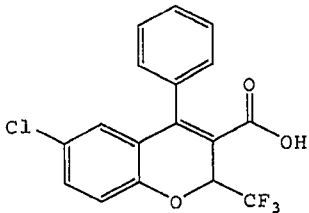
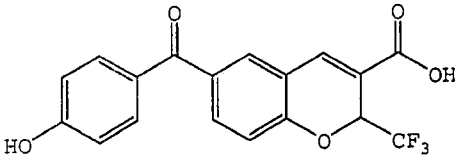
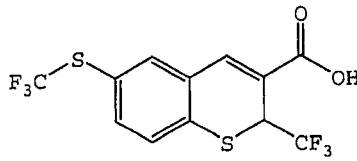
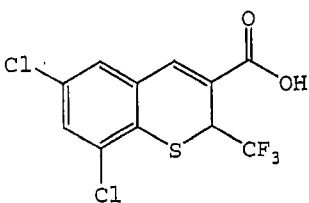
30 R^{23} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, tert-butyl, difluoromethoxy, and phenyl;

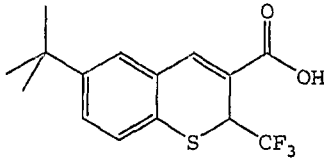
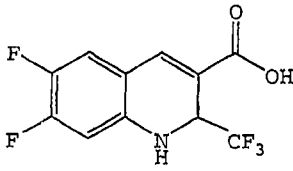
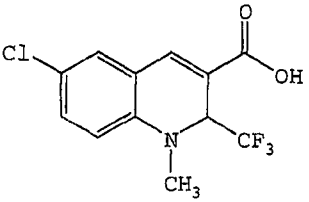
or an isomer or prodrug thereof.

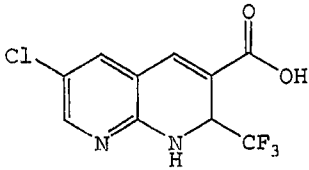
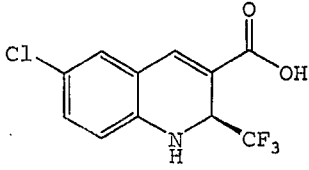
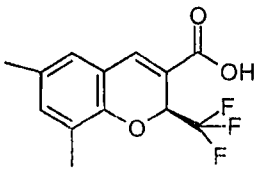
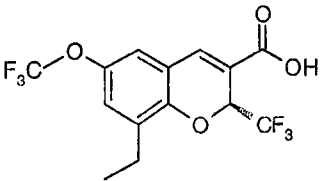
Table 1 Examples of Chromene Cox-2 Selective Inhibitors

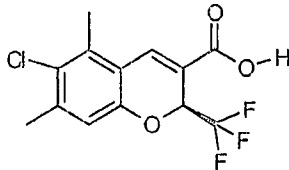
Compound Number	Structural Formula
B-3	 6-Nitro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-4	 6-Chloro-8-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-5	 (R)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-6	 2-(Trifluoromethyl)-2H-naphtho[2,3-b]pyran-3-carboxylic acid
B-7	 6-chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-8	 6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

<u>Compound Number</u>	<u>Structural Formula</u>
B-9	 6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid
B-10	 6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-11	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid
B-12	 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid

<u>Compound Number</u>	<u>Structural Formula</u>
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoromethyl)-3-quinolinecarboxylic acid

<u>Compound</u> <u>Number</u>	<u>Structural Formula</u>
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro[1,8]naphthyridine-3-carboxylic acid
B-17	 ((S)-6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid
B-18	 (2S)-6,8-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid
B-19	 (2S)-8-ethyl-6-(trifluoromethoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid

<u>Compound Number</u>	<u>Structural Formula</u>
B-20	 (2S)-6-chloro-5,7-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid

[000102] In preferred embodiments, the chromene Cox-2 inhibitor is comprises at least one compound selected from the group consisting of

6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid,

7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

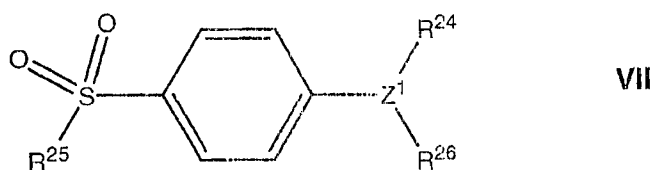
- 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 5 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid,
 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 10 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 15 6-[[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-
 carboxylic acid,
 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-
 carboxylic acid,
 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic
 20 acid,
 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic
 acid,
 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-
 carboxylic acid,
 25 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-
 carboxylic acid,
 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 8-chloro-6-[[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-
 benzopyran-3-carboxylic acid,
 30 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

- 6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-
 carboxylic acid,
 5 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-
 carboxylic acid,
 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic
 acid,
 10 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid.
 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 (S)-6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-
 carboxylic acid,
 15 (S)-6-chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-
 carboxylic acid,
 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 (S)-6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic
 acid,
 20 6-formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
 6-(difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
 6,8-dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic
 acid,
 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 25 (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
 6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
 (S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
 6,8-dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 30 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
 5,6-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
 2,6-bis(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

5,6,7-trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
 6,7,8-trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
 6-iodo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
 6-bromo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
 5 6-chloro-7-methyl-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic
 acid,
 6,8-dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid, and
 mixtures thereof.

10 **[000103]** In further preferred embodiments, the chromene Cox-2
 inhibitor is selected from (S)-6-chloro-7-(1,1-dimethylethyl)-2-
 (trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, (2S)-6,8-dimethyl-2-
 (trifluoromethyl)-2H-chromene-3-carboxylic acid, (2S)-6-chloro-8-methyl-2-
 (trifluoromethyl)-2H-chromene-3-carboxylic acid, (2S)-8-ethyl-6-
 (trifluoromethoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (S)-
 15 6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, (2S)-6-
 chloro-5,7-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, and
 mixtures thereof.

20 **[000104]** In a preferred embodiment of the invention, the Cox-2 inhibitor
 can be selected from the class of tricyclic Cox-2 selective inhibitors
 represented by the general structure of formula VII:



25 wherein:
 Z¹ is selected from the group consisting of partially unsaturated or
 unsaturated heterocyclyl and partially unsaturated or unsaturated
 carbocyclic rings;
 R²⁴ is selected from the group consisting of heterocyclyl, cycloalkyl,
 cycloalkenyl and aryl, wherein R²⁴ is optionally substituted at a

substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

5 R^{25} is selected from the group consisting of methyl or amino; and

R^{26} is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N- arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N- arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-aryl amino, aminoalkyl, alkylaminoalkyl, N-arylaminalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N- arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

10 or a prodrug thereof.

20 **[000105]** In a preferred embodiment of the invention, the tricyclic Cox-2 selective inhibitor comprises at least one compound selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, lumiracoxib, etoricoxib, rofecoxib, prodrugs of any of them, and mixtures thereof.

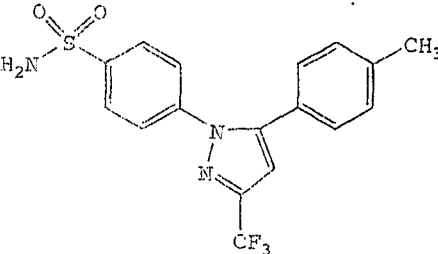
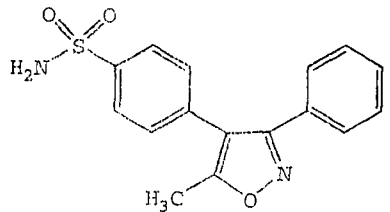
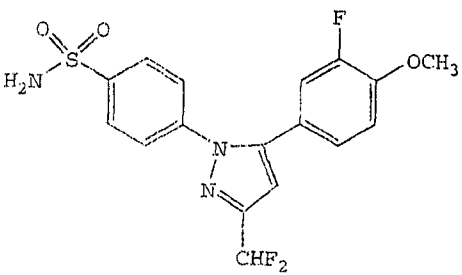
25 **[000106]** In a further preferred embodiment of the invention, the Cox-2 selective inhibitor represented by the above Formula VII is selected from the group of compounds, illustrated in Table 2, which includes celecoxib (B-21), valdecoxib (B-22), deracoxib (B-23), rofecoxib (B-24), etoricoxib (MK-663; B-25), JTE-522 (B-26), or prodrugs thereof.

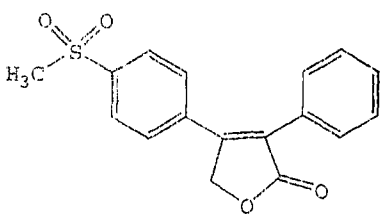
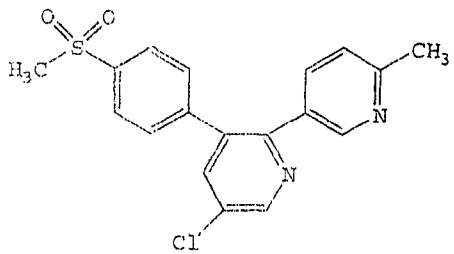
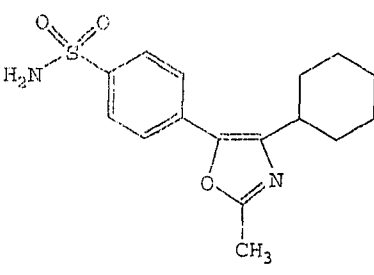
30 **[000107]** Additional information about selected examples of the Cox-2 selective inhibitors discussed above can be found as follows: celecoxib

(CAS RN 169590-42-5, C-2779, SC-58653, and in U.S. Patent No. 5,466,823); deracoxib (CAS RN 169590-41-4); rofecoxib (CAS RN 162011-90-7); compound B-24 (U.S. Patent No. 5,840,924); compound B-26 (WO 00/25779); and etoricoxib (CAS RN 202409-33-4, MK-663, SC-86218, and in WO 98/03464).

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Table 2. Examples of Tricyclic Cox-2 Selective Inhibitors

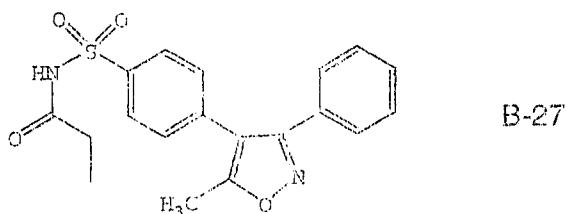
<u>Compound Number</u>	<u>Structural Formula</u>
B-21	 <chem>CC1=CC=C(C=C1)c2nc(C(F)(F)F)cnn2Nc3ccc(S(=O)(=O)N)cc3</chem>
B-22	 <chem>Cc1nc2ccccc2no1C3=CC=C(C=C3)S(=O)(=O)N</chem>
B-23	 <chem>COc1cc(F)ccc1C2=CN=C(NC3=CC=C(C=C3)S(=O)(=O)N)N2C(F)F</chem>

<u>Compound Number</u>	<u>Structural Formula</u>
B-24	
B-25	
B-26	

[000108] In a more preferred embodiment of the invention, the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

5 [000109] In a preferred embodiment, parecoxib (See, U.S. Patent No. 5,932,598), having the structure shown in B-27, and which is a therapeutically effective prodrug of the tricyclic Cox-2 selective inhibitor

valdecoxib, B-22, (See, U.S. Patent No. 5,633,272), may be advantageously employed as the Cox-2 inhibitor of the present invention.

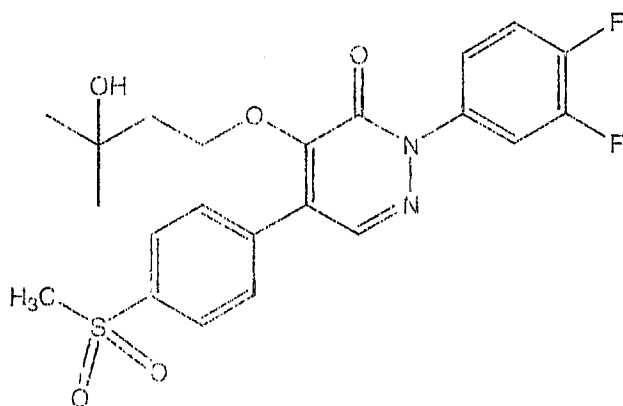


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[000110] A preferred form of parecoxib is sodium parecoxib.

[000111] Another tricyclic Cox-2 selective inhibitor useful in the present invention is the compound ABT-963, having the formula B-28 shown below, that has been previously described in International Publication Number WO 00/24719.

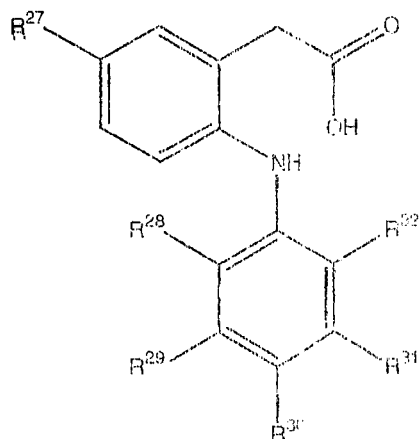
10



B-28

15

[000112] In a further embodiment of the invention, the Cox-2 inhibitor can be selected from the class of phenylacetic acid derivative Cox-2 selective inhibitors represented by the general structure of formula VIII:



VIII

wherein:

R^{27} is methyl, ethyl, or propyl;

5 R^{28} is chloro or fluoro;

R^{29} is hydrogen, fluoro, or methyl;

R^{30} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxyl;

R^{31} is hydrogen, fluoro, or methyl; and

R^{32} is chloro, fluoro, trifluoromethyl, methyl, or ethyl,

10 provided that R^{28} , R^{29} , R^{30} and R^{31} are not all fluoro when R^{27} is ethyl and R^{30} is H.

[000113] An exemplary phenylacetic acid derivative Cox-2 selective inhibitor that is described in WO 99/11605 is a compound that has the structure shown in formula VIII,

15 wherein:

R^{27} is ethyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are hydrogen; and

R^{32} is methyl.

20 [000114] Another phenylacetic acid derivative Cox-2 selective inhibitor is a compound that has the structure shown in formula VIII,

wherein:

R^{27} is propyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are methyl; and

R^{32} is ethyl.

[000115] Another phenylacetic acid derivative Cox-2 selective inhibitor that is disclosed in WO 02/20090 is a compound that is referred to as Cox-189 (also termed lumiracoxib, CAS Reg. No. 220991-20-8), having the structure shown in formula VIII,

wherein:

R^{27} is methyl;

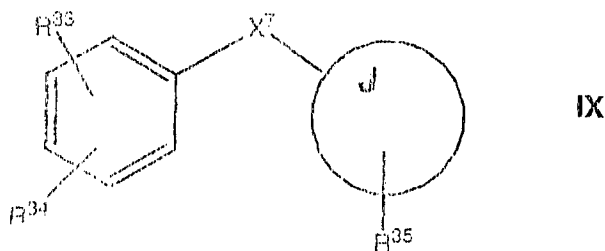
R^{28} is fluoro;

R^{32} is chloro; and

R^{29} , R^{30} , and R^{31} are hydrogen.

[000116] Compounds having a structure similar to that shown in formula VIII, that can serve as the Cox-2 selective inhibitor of the present invention, are described in U.S. Patent Nos. 6,451,858, 6,310,099, 6,291,523, and 5,958,978.

[000117] Other Cox-2 selective inhibitors that can be used in the present invention have the general structure shown in formula IX, where the J group is a carbocycle or a heterocycle. Preferred embodiments have the structure:



wherein:

X^7 is O; J is 1-phenyl; R^{33} is 2-NHSO₂CH₃; R^{34} is 4-NO₂; and there is no R^{35} group, (nimesulide), or

X^7 is O; J is 1-oxo-inden-5-yl; R^{33} is 2-F; R^{34} is 4-F; and R^{35} is 6-NHSO₂CH₃, (flosulide); or

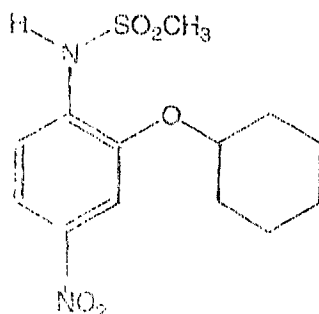
X^7 is O; J is cyclohexyl; R^{33} is 2-NHSO₂CH₃; R^{34} is 5-NO₂; and there is no R^{35} group, (NS-398); or

X^7 is S; J is 1-oxo-inden-5-yl; R^{33} is 2-F; R^{34} is 4-F; and R^{35} is 6-NHSO₂CH₃ · Na⁺, (L-745337); or

5 X^7 is S; J is thiophen-2-yl; R^{33} is 4-F; there is no R^{34} group; and R^{35} is 5-NHSO₂CH₃, (FWJ-63556); or

X^7 is O; J is 2-oxo-5(methyl-5-(2,2,2-trifluoroethyl)furan-(5H)-3-yl; R^{33} is 3-F; R^{34} is 4-F; and R^{35} is 4-(p-SO₂CH₃)C₆H₄, (L-784512).

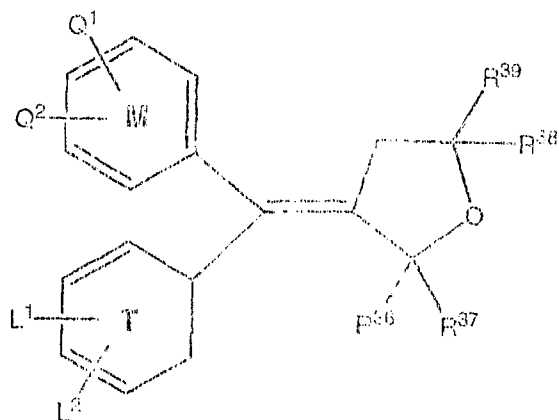
10 [000118] The Cox-2 selective inhibitor NS-398, also known as N-(2-cyclohexyloxynitrophenyl) methane sulfonamide (CAS RN 123653-11-2), having a structure as shown below in formula B-29, has been described in, for example, Yoshimi N. *et al.*, in *Japanese J. Cancer Res.*, 90(4):406-412 (1999).



B-29

20 [000119] An evaluation of the anti-inflammatory activity of the Cox-2 selective inhibitor, FWJ 63556, in a canine model of inflammation, was described by Kirchner *et al.*, in *J Pharmacol Exp Ther* 282, 1094-1101 (1997).

25 [000120] Materials that can serve as the Cox-2 selective inhibitor of the present invention include diarylmethylidenefuran derivatives that are described in U.S. Patent No. 6,180,651. Such diarylmethylidenefuran derivatives have the general formula shown below in formula X:



wherein:

the rings T and M independently are a phenyl radical, a naphthyl radical, a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

at least one of the substituents Q¹, Q², L¹ or L² is an —S(O)_n—R group, in which n is an integer equal to 0, 1 or 2 and R is a lower alkyl radical having 1 to 6 carbon atoms, a lower haloalkyl radical having 1 to 6 carbon atoms, or an —SO₂NH₂ group;

and is located in the para position,

the others independently being a hydrogen atom, a halogen atom, a lower alkyl radical having 1 to 6 carbon atoms, a trifluoromethyl radical, or a lower O-alkyl radical having 1 to 6 carbon atoms, or Q¹ and Q² or L¹ and L² are a methylenedioxy group; and

R³⁶, R³⁷, R³⁸ and R³⁹ independently are a hydrogen atom, a halogen atom, a lower alkyl radical having 1 to 6 carbon atoms, a lower haloalkyl radical having 1 to 6 carbon atoms, or an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R³⁶, R³⁷ or R³⁸, R³⁹ are an oxygen atom; or

R³⁶, R³⁷ or R³⁸, R³⁹, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

or an isomer or prodrug thereof.

[000121] Particular diary methylenesulfon derivatives that can serve as the Cox-2 selective inhibitor of the present invention include, for example, N-(2-cyclohexyloxyphenyl)methanesulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene)

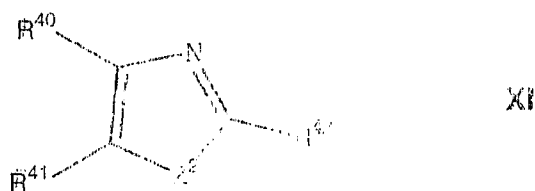
5 methylbenzenesulfonamide

[000122] Other Cox-2 selective inhibitors that are useful in the present invention include dactofensin (Pfizer), GS-502 (Sankyo), LAS 34475 (Almirall Profrstarma), LAS 34555 (Almirall Profrstarma), S-33516 (Servier), SD 1331 (Pharmacia, described in U.S. Patent No. 6,034,256), BMS-347070 (Bristol Myers Squibb, described in U.S. Patent No. 10 6,180,651), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1367 (Chiroscience), L-744731 (Merck), CT3 (Atlantic Pharmaceutical), CGP-28238 (Novartis), BF-389 (Dietor/Schering), GE 253035 (Glaxo Wellcome), 6-dioxo-9H-purin-8-ylideneacetic acid (Glaxo Wellcome), and S-2474 (Shionogi).

[000123] Compounds that may act as Cox-2 selective inhibitors of the present invention include multibinding compounds containing from 2 to 10 15 ligands covalently attached to one or more linkers, as described in U.S. Patent No. 6,395,724.

[000124] Conjugated linoleic, as described in U.S. Patent No. 20 6,077,868, is useful as a Cox-2 selective inhibitor in the present invention.

[000125] Compounds that can serve as a Cox-2 selective inhibitor of the present invention include heterocyclic aromatic oxazole compounds that are described in U.S. Patents 5,994,381 and 6,362,209. Such heterocyclic 25 aromatic oxazole compounds have the formula shown below in formula XI:

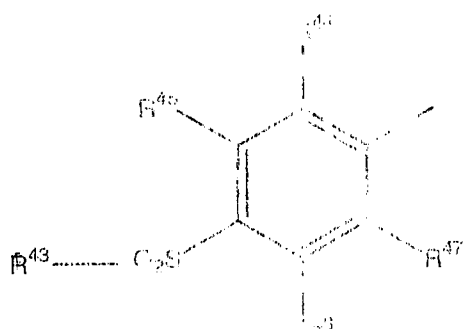


Wherein:

Z^2 is an oxygen atom;

one of R^{40} and R^{41} is a group of the formula

5



Wherein:

R^{43} is lower alkyl, amino or lower alkylamino; and

10

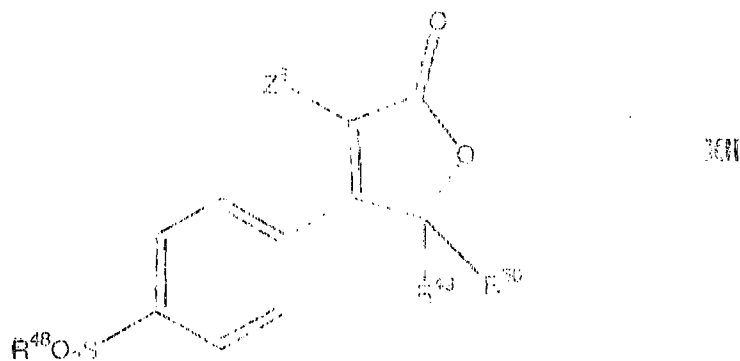
R^{44} , R^{45} , R^{46} and R^{47} are the same or different and each is hydrogen atom, halogen atom, lower alkyl, lower alkoxy, trifluoromethyl, hydroxyl or amino, provided that at least one of R^{44} , R^{45} , R^{46} and R^{47} is not hydrogen atom, and the other is an optionally substituted cycloalkyl, an optionally substituted heterocyclic group or an optionally substituted aryl; and

15

R^{40} is a lower alkyl or a halogenated lower alkyl, and a pharmaceutically acceptable salt thereof.

[000126] Cox-2 selective inhibitors that are useful in the method and compositions of the present invention include compounds that are described in U.S. Patent Nos. 6,030,676 and 6,133,292, and described by formula (33):

20



wherein:

Z^3 is selected from the group consisting of linear or branched C_1-C_6 alkyl, linear or branched C_1-C_6 alkoxy, unsubstituted, mono-, di- or tri-substituted phenyl or naphthyl, wherein the substituents are selected from the group consisting of hydrogen, halo, C_1-C_2 alkoxy, CN, C_1-C_3 fluoroalkyl, C_1-C_3 alkyl, and $-CO_2H$.

R^{48} is selected from the group consisting of NH_2 and CH_3 .

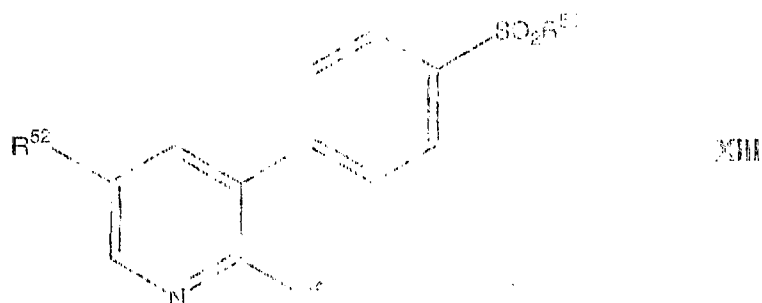
R^{49} is selected from the group consisting of C_1-C_3 alkyl unsubstituted or substituted with C_1-C_2 cycloalkyl, and C_6-C_8 cycloalkyl;

R^{50} is selected from the group consisting of:

C_1-C_6 alkyl unsubstituted or substituted with one, two or three fluorine atoms, and C_6-C_8 cycloalkyl;

with the proviso that R^{49} and R^{50} are not the same.

[000127] Pyridines that are described in U.S. Patent Nos. 6,596,736; 6,362,275; 6,127,545; 6,122,334; 6,204,587; 6,071,936; 6,001,843 and 6,040,450, and can serve as Cox-2 selective inhibitors of the present invention, have the general formula described by formula XIII:



wherein:

R^{51} is selected from a group consisting of CH_3 , NH_2 , $NHC(O)CF_3$, and $NHCH_3$;

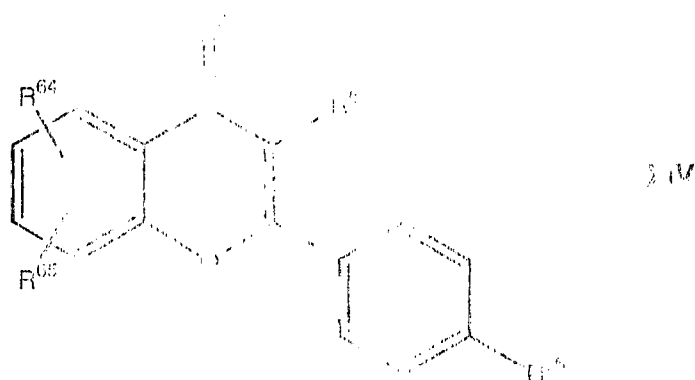
Z^4 is a mono-, di-, or trifluoromethylated phenyl or pyridinyl (or the N-oxide thereof), wherein the substituents are chosen from the group consisting of hydrogen, halo, C_1-C_6 alkoxy, C_1-C_6 alkylthio, CN, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, N_3 , $-CO_2R^{56}$, $-C(R^{56})(R^{55})-OH$, $-C_1-C_6$ alkyl- CO_2R^{56} , C_1-C_6 thioalkoxy;

R^{52} is chosen from the group consisting of halo, C_1-C_6 alkoxy, C_1-C_6 alkylthio, CN, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, N_3 , $-CO_2R^{57}$, hydroxyl, $-C(R^{58})(R^{59})-OH$, $-C_1-C_6$ alkyl- CO_2R^{58} , C_1-C_6 fluoroalkoxy, NO_2 , $NR^{61}R^{62}$, and $NHC(O)R^{63}$;

R^{53} , R^{54} , R^{55} , R^{56} , R^{57} , R^{58} , R^{59} , R^{60} , R^{61} , R^{62} , and R^{63} , are each independently chosen from a group consisting of hydrogen and C_1-C_6 alkyl;

or R^{53} and R^{54} , R^{55} and R^{56} , or R^{57} and R^{58} together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6, or 7 atoms;

[000742] Alternately, the compound can serve as the Cox-2 selective inhibitor of the present invention in the form of benzopyran derivatives that are described in U.S. Patent No. 6,140,600. Such diarylbenzopyran derivatives have the general formula shown in formula (I):



wherein:

X^8 is an oxygen atom or a sulfur atom;

R^{64} and R^{65} , identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_1-C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a nitro group, a nitrite group, or a carboxyl group;

R^{66} is a group of a formula: $B(O)_nR^{68}$ wherein n is an integer of 0~2, R^{68} is

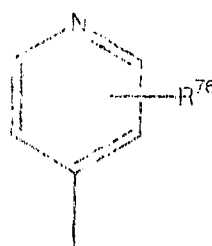
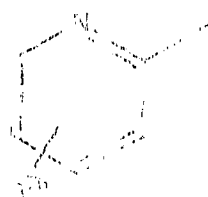
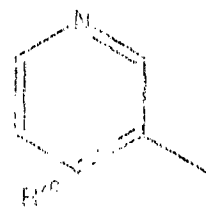
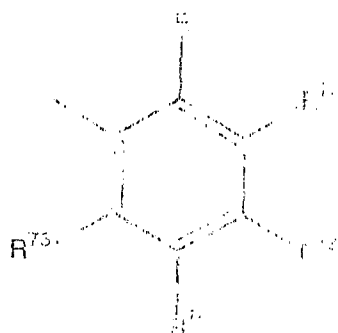
a hydrogen atom, a C_1-C_6 lower alkyl group, or a group of a formula: NR^{69}

R^{70} wherein R^{68} and R^{69} , identical to or different from each other, are

independently a hydrogen atom, or a C_1-C_6 lower alkyl group; and

R^{67} is oxazolyl, benzoxazolyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzoxazolyl, pyrazolyl, pyrazolyl substituted with a C_1-C_6 lower alkyl group, a phenyl group, or a substituted group represented by the

following structure:



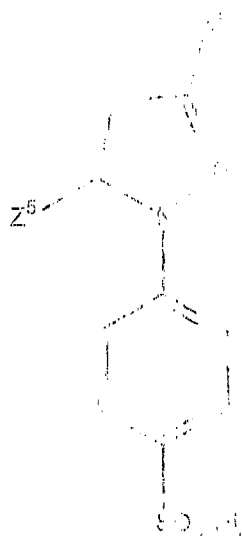
wherein

5 R^{71} through R^{75} , identical or different from one another, are independently a hydrogen atom, a halogen atom, a C_1 - C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a hydroxyalkyl group, a nitrile group, a group of a formula: $S(O)_nR^{68}$, a group of a formula: OR^{69} , a bromomethoxy group, a nitrile group, a carboxyl group, an acetyl group, or a formyl group.

10 wherein R^{68} , R^{69} , and R^{76} have the same meaning as defined by R^{66} above; and

R^{76} is a hydrogen atom, a hydrogen atom, a C_1 - C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a trifluoromethyl group, a carboxyl group, or an acetyl group.

15 [00079] The compound of the present invention serves as the Cox-2 selective inhibitor of the present invention. The 1-(4-sulfamoyl)-3-substituted-5-aryl-2-pyrazones have been disclosed in U.S. Patent No. 6,376,519. Such 1-(4-sulfamoyl)-3-substituted-5-aryl-2-pyrazones have the formula shown below in formula (34).

X⁶

wherein:

- 5 X⁶ is a substituent group consisting of C₁-C₃ trihalomethyl, preferably trifluoromethyl, or an optionally substituted or di-substituted phenyl group, formula (X⁶).

X⁷

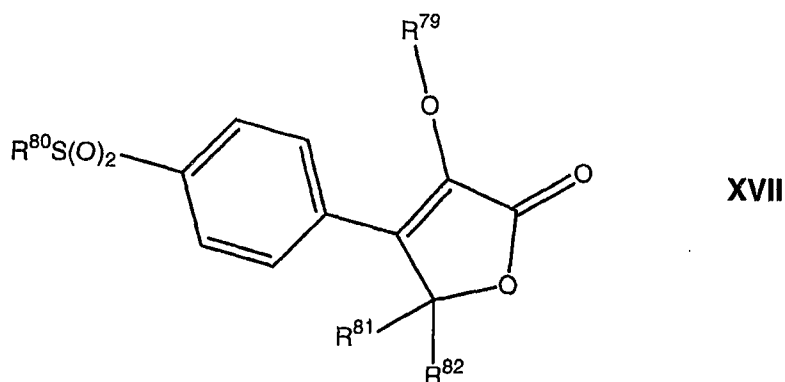
10

wherein:

- R¹ and R² are independently selected from the group consisting of
 hydrogen, halogen, chlorine, fluorine and bromine; hydroxyl;
 nitro; C₁-C₃ alkyl; C₁-C₃ alkoxy; C₁-C₃ alkyl; C₁-C₃ alkoxy, preferably C₁-
 15 C₃ alkyl; C₁-C₃ alkoxy; C₁-C₃ alkyl; C₁-C₃ alkoxy, preferably trifluoromethyl, most
 preferably trifluoromethyl, or a substituent group.

Z^5 is selected from the group consisting of substituted and unsubstituted aryl.

[000130] Compounds useful as Cox-2 selective inhibitors of the present invention include heterocycles that are described in U.S. Patent No. 6,153,787. Such heterocycles have the general formulas shown below in formulas **XVII** and **XVIII**:



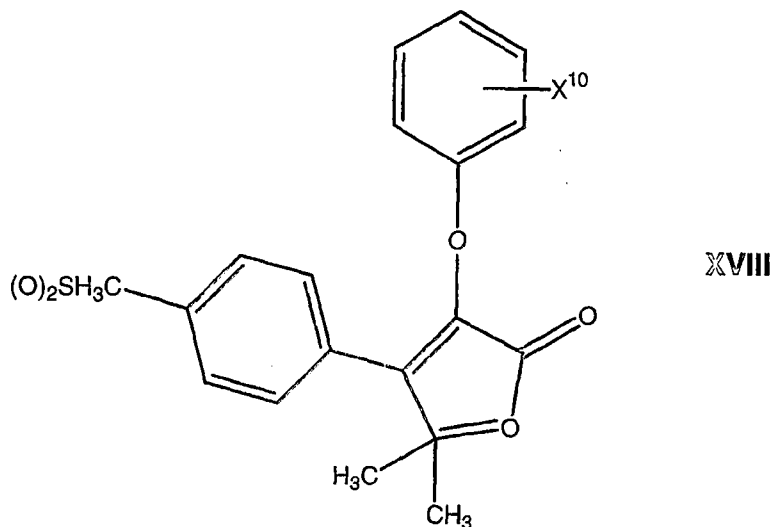
wherein:

R^{79} is a mono-, di-, or tri-substituted $C_1 - C_{12}$ alkyl, or a mono-, or an unsubstituted or mono-, di- or tri-substituted linear or branched $C_2 - C_{10}$ alkenyl, or an unsubstituted or mono-, di- or tri-substituted linear or branched $C_2 - C_{10}$ alkynyl, or an unsubstituted or mono-, di- or tri-substituted $C_3 - C_{12}$ cycloalkenyl, or an unsubstituted or mono-, di- or tri-substituted $C_5 - C_{12}$ cycloalkynyl, wherein the substituents are chosen from the group consisting of halo selected from F, Cl, Br, and I, OH, CF_3 , $C_3 - C_6$ cycloalkyl, $=O$, dioxolane, CN;

R^{80} is selected from the group consisting of CH_3 , NH_2 , $NHC(O)CF_3$, and $NHCH_3$;

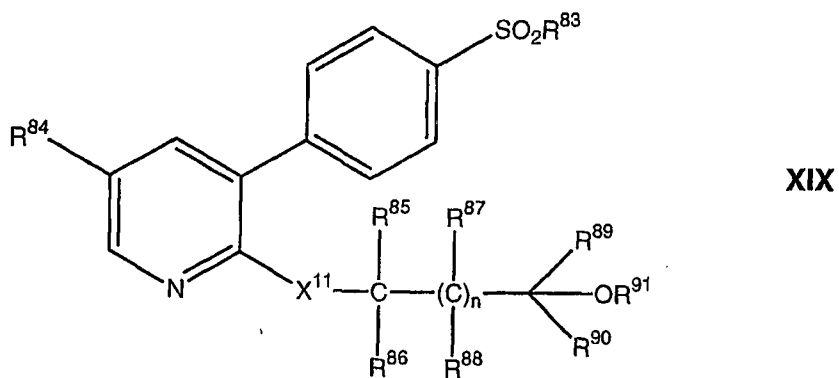
R^{81} and R^{82} are independently chosen from the group consisting of hydrogen and $C_1 - C_{10}$ alkyl; or R^{81} and R^{82} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms.

[000131] Formula **XVIII** is:



wherein X^{10} is fluoro or chloro.

5 **[000132]** Materials that can serve as the Cox-2 selective inhibitor of the present invention include 2,3,5-trisubstituted pyridines that are described in U.S. Patent No. 6,046,217. Such pyridines have the general formula shown below in formula **XIX**:



10

or a pharmaceutically acceptable salt thereof,
wherein:

X^{11} is selected from the group consisting of O, S, and a bond;
 n is 0 or 1;

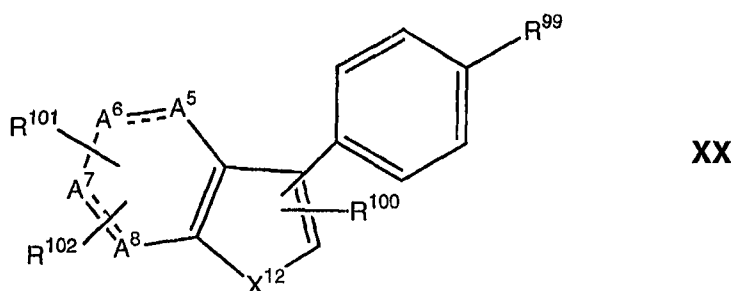
R^{83} is selected from the group consisting of CH_3 , NH_2 , and $NHC(O)CF_3$;

R^{84} is chosen from the group consisting of halo, $C_1 - C_6$ alkoxy, $C_1 - C_6$ alkylthio, CN, $C_1 - C_6$ alkyl, $C_1 - C_6$ fluoroalkyl, N_3 , $-CO_2 R^{92}$, hydroxyl, $-C(R^{93})(R^{94})-OH$, $-C_1 - C_6$ alkyl- $CO_2 - R^{95}$, $C_1 - C_6$ fluoroalkoxy, NO_2 , $NR^{96} R^{97}$, and $NHCOR^{98}$;

R^{85} to R^{89} are independently chosen from the group consisting of hydrogen and $C_1 - C_6$ alkyl;

or R^{85} and R^{89} , or R^{89} and R^{90} together with the atoms to which they are attached form a carbocyclic ring of 3, 4, 5, 6 or 7 atoms, or R^{85} and R^{87} are joined to form a bond.

[000133] Compounds that are useful as the Cox-2 selective inhibitor of the present invention include diaryl bicyclic heterocycles that are described in U.S. Patent No. 6,329,421. Such diaryl bicyclic heterocycles have the general formula shown below in formula **XX**:



and pharmaceutically acceptable salts thereof wherein:

$-A^5=A^6-A^7=A^8-$ is selected from the group consisting of:

(a) $-CH=CH-CH=CH-$,

(b) $-CH_2-CH_2-CH_2-C(O)-$, $-CH_2-CH_2-C(O)-CH_2-$, $-CH_2-C(O)-CH_2-CH_2-$, $-C(O)-CH_2-CH_2-CH_2-$,

(c) $-CH_2-CH_2-C(O)-$, $-CH_2-C(O)-CH_2-$, $-C(O)-CH_2-CH_2-$

(d) $-CH_2-CH_2-O-C(O)-$, $CH_2-O-C(O)-CH_2-$, $-O-C(O)-CH_2-CH_2-$,

- (e) $-\text{CH}_2-\text{CH}_2-\text{C}(\text{O})-\text{O}-$, $-\text{CH}_2-\text{C}(\text{O})-\text{OCH}_2-$, $-\text{C}(\text{O})-\text{O}-\text{CH}_2-\text{CH}_2-$,
 (f) $-\text{C}(\text{R}^{105})_2-\text{O}-\text{C}(\text{O})-$, $-\text{C}(\text{O})-\text{O}-\text{C}(\text{R}^{105})_2-$, $-\text{O}-\text{C}(\text{O})-\text{C}(\text{R}^{105})_2-$, $-\text{C}(\text{R}^{105})_2-\text{C}(\text{O})-\text{O}-$,
 5 (g) $-\text{N}=\text{CH}-\text{CH}=\text{CH}-$,
 (h) $-\text{CH}=\text{N}-\text{CH}=\text{CH}-$,
 (i) $-\text{CH}=\text{CH}-\text{N}=\text{CH}-$,
 (j) $-\text{CH}=\text{CH}-\text{CH}=\text{N}-$,
 (k) $-\text{N}=\text{CH}-\text{CH}=\text{N}-$,
 10 (l) $-\text{N}=\text{CH}-\text{N}=\text{CH}-$,
 (m) $-\text{CH}=\text{N}-\text{CH}=\text{N}-$,
 (n) $-\text{S}-\text{CH}=\text{N}-$,
 (o) $-\text{S}-\text{N}=\text{CH}-$,
 (p) $-\text{N}=\text{N}-\text{NH}-$,
 15 (q) $-\text{CH}=\text{N}-\text{S}-$, and
 (r) $-\text{N}=\text{CH}-\text{S}-$;
 R^{99} is selected from the group consisting of $\text{S}(\text{O})_2\text{CH}_3$, $\text{S}(\text{O})_2\text{NH}_2$,
 $\text{S}(\text{O})_2\text{NHCOCF}_3$, $\text{S}(\text{O})(\text{NH})\text{CH}_3$, $\text{S}(\text{O})(\text{NH})\text{NH}_2$, $\text{S}(\text{O})(\text{NH})\text{NHCOCF}_3$,
 $\text{P}(\text{O})(\text{CH}_3)\text{OH}$, and $\text{P}(\text{O})(\text{CH}_3)\text{NH}_2$;
 20 R^{100} is selected from the group consisting of:
 (a) C_1-C_6 alkyl,
 (b) C_3-C_7 cycloalkyl,
 (c) mono- or di-substituted phenyl or naphthyl wherein the substituent is
 selected from the group consisting of:
 25 (1) hydrogen,
 (2) halo, including F, Cl, Br, I,
 (3) C_1-C_6 alkoxy,
 (4) C_1-C_6 alkylthio,
 (5) CN,
 30 (6) CF_3 ,
 (7) C_1-C_6 alkyl,
 (8) N_3 ,

(9) $-\text{CO}_2 \text{ H}$,

(10) $-\text{CO}_2 -\text{C}_1 -\text{C}_4 \text{ alkyl}$,

(11) $-\text{C}(\text{R}^{103})(\text{R}^{104})-\text{OH}$,

(12) $-\text{C}(\text{R}^{103})(\text{R}^{104})-\text{O}-\text{C}_1 -\text{C}_4 \text{ alkyl}$, and

5 (13) $-\text{C}_1 -\text{C}_6 \text{ alkyl}-\text{CO}_2 -\text{R}^{106}$;

(d) mono- or di-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) $\text{C}_1 -\text{C}_6 \text{ alkyl}$,

15 (4) $\text{C}_1 -\text{C}_6 \text{ alkoxy}$,

(5) $\text{C}_1 -\text{C}_6 \text{ alkylthio}$,

(6) CN,

(7) CF_3 ,

(8) N_3 ,

20 (9) $-\text{C}(\text{R}^{103})(\text{R}^{104})-\text{OH}$, and

(10) $-\text{C}(\text{R}^{103})(\text{R}^{104})-\text{O}-\text{C}_1 -\text{C}_4 \text{ alkyl}$;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^{101} and R^{102} are the substituents residing on any position of $-\text{A}^5=\text{A}^6-$ $\text{A}^7=\text{A}^8-$ and are selected independently from the group consisting of:

25 (a) hydrogen,

(b) CF_3 ,

(c) CN,

(d) $\text{C}_1 -\text{C}_6 \text{ alkyl}$,

(e) $-\text{Q}^3$ wherein Q^3 is Q^4 , $\text{CO}_2 \text{ H}$, $\text{C}(\text{R}^{103})(\text{R}^{104})\text{OH}$,

30 (f) $-\text{O}-\text{Q}^4$,

(g) $-\text{S}-\text{Q}^4$, and

(h) optionally substituted:

- (1) $-\text{C}_1-\text{C}_5$ alkyl- Q^3 ,
 (2) $-\text{O}-\text{C}_1-\text{C}_5$ alkyl- Q^3 ,
 (3) $-\text{S}-\text{C}_1-\text{C}_5$ alkyl- Q^3 ,
 (4) $-\text{C}_1-\text{C}_3$ alkyl- $\text{O}-\text{C}_{1-3}$ alkyl- Q^3 ,
 (5) $-\text{C}_1-\text{C}_3$ alkyl- $\text{S}-\text{C}_{1-3}$ alkyl- Q^3 ,
 (6) $-\text{C}_1-\text{C}_5$ alkyl- $\text{O}-\text{Q}^4$,
 (7) $-\text{C}_1-\text{C}_5$ alkyl- $\text{S}-\text{Q}^4$,

wherein the substituent resides on the alkyl chain and the substituent is C_1-C_3 alkyl, and Q^3 is Q^4 , CO_2H , $\text{C}(\text{R}^{103})(\text{R}^{104})\text{OH}$ Q^4 is $\text{CO}_2-\text{C}_1-\text{C}_4$ alkyl, tetrazolyl-5-yl, or $\text{C}(\text{R}^{103})(\text{R}^{104})\text{O}-\text{C}_1-\text{C}_4$ alkyl;

R^{103} , R^{104} and R^{105} are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; or

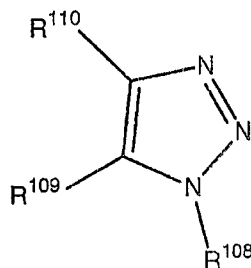
R^{103} and R^{104} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms, or two R^{105} groups on the same carbon form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R^{106} is hydrogen or C_1-C_6 alkyl;

R^{107} is hydrogen, C_1-C_6 alkyl or aryl;

X^7 is O, S, NR^{107} , CO, $\text{C}(\text{R}^{107})_2$, $\text{C}(\text{R}^{107})(\text{OH})$, $-\text{C}(\text{R}^{107})=\text{C}(\text{R}^{107})-$; $-\text{C}(\text{R}^{107})=\text{N}-$; or $-\text{N}=\text{C}(\text{R}^{107})-$.

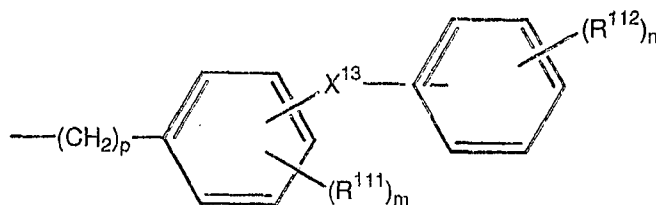
[000134] Compounds that may act as Cox-2 selective inhibitors include salts of 5-amino or a substituted amino 1,2,3-triazole compound that are described in U.S. Patent No. 6,239,137. The salts are of a class of compounds of formula **XXI**:



XXI

wherein:

R^{108} is:



5

wherein:

p is 0 to 2; m is 0 to 4; and n is 0 to 5;

X^{13} is O, S, SO, SO₂, CO, CHCN, CH₂ or C=NR¹¹³ where R^{113} is hydrogen, loweralkyl, hydroxyl, loweralkoxy, amino, loweralkylamino, diloweralkylamino or cyano;

10

R^{111} and R^{112} are independently halogen, cyano, trifluoromethyl, loweralkanoyl, nitro, loweralkyl, loweralkoxy, carboxy, lowercarbalkoxy, trifluoromethoxy, acetamido, loweralkylthio, loweralkylsulfinyl, loweralkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, or trifluoromethylsulfonyl;

15

R^{109} is amino, mono or diloweralkyl amino, acetamido, acetimido, ureido, formamido, or guanidino; and

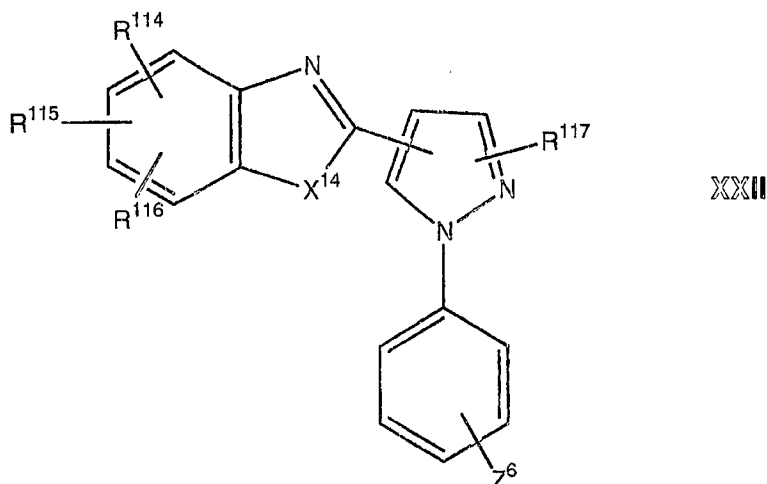
R^{110} is carbamoyl, cyano, carbazoyl, amidino or N-hydroxycarbamoyl;

wherein the loweralkyl, loweralkyl containing, loweralkoxy and

20

loweralkanoyl groups contain from 1 to 3 carbon atoms.

[000135] Pyrazole derivatives such as those described in U.S. Patent 6,136,831 can serve as a Cox-2 selective inhibitor of the present invention. Such pyrazole derivatives have the formula shown below in formula XXII:



wherein:

R^{114} is hydrogen or halogen;

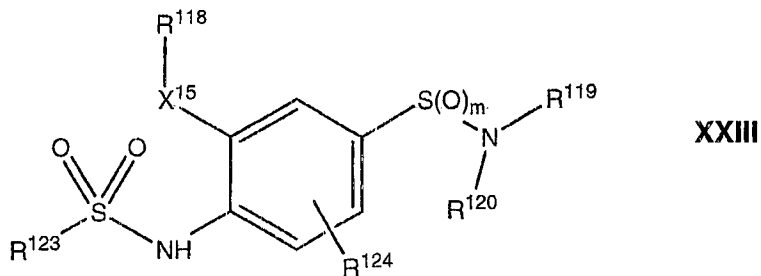
R^{115} and R^{116} are each independently hydrogen, halogen, lower alkyl,
5 lower alkoxy, hydroxyl or lower alkanoyloxy;

R^{117} is lower haloalkyl or lower alkyl;

X^{14} is sulfur, oxygen or NH; and

Z^6 is lower alkylthio, lower alkylsulfonyl or sulfamoyl;
or a pharmaceutically acceptable salt thereof.

10 **[000136]** Materials that can serve as a Cox-2 selective inhibitor of the present invention include substituted derivatives of benzosulphonamides that are described in U.S. Patent 6,297,282. Such benzosulphonamide derivatives have the formula shown below in formula **XXIII**:



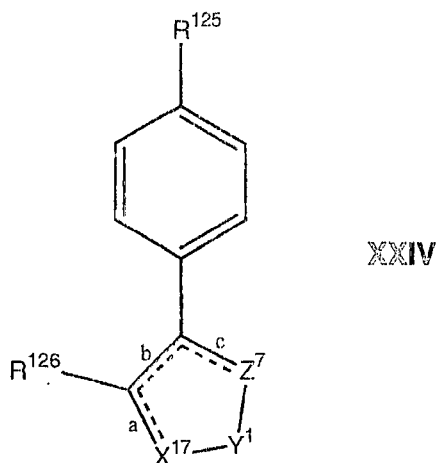
15 wherein:

X^{15} denotes oxygen, sulphur or NH;

- 5 R^{118} is an optionally unsaturated alkyl or alkyloxyalkyl group, optionally mono- or polysubstituted or mixed substituted by halogen, alkoxy, oxo or cyano, a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted or mixed substituted by halogen, alkyl, CF_3 , cyano or alkoxy;
- R^{119} and R^{120} , independently from one another, denote hydrogen, an optionally polyfluorised alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n - X^{16}$; or
- 10 R^{119} and R^{120} , together with the N- atom, denote a 3 to 7-membered, saturated, partially or completely unsaturated heterocycle with one or more heteroatoms N, O or S, which can optionally be substituted by oxo, an alkyl, alkylaryl or aryl group, or a group $(CH_2)_n - X^{16}$;
- X^{16} denotes halogen, NO_2 , $-OR^{121}$, $-COR^{121}$, $-CO_2 R^{121}$, $-OCO_2 R^{121}$, $-CN$, $-CONR^{121} OR^{122}$, $-CONR^{121} R^{122}$, $-SR^{121}$, $-S(O)R^{121}$, $-S(O)_2 R^{121}$, $-NR^{121} R^{122}$, $-NHC(O)R^{121}$, $-NHS(O)_2 R^{121}$;
- 15 n denotes a whole number from 0 to 6;
- R^{123} denotes a straight-chained or branched alkyl group with 1-10 C-atoms, a cycloalkyl group, an alkylcarboxyl group, an aryl group, aralkyl group, a heteroaryl or heteroaralkyl group which can optionally be mono- or polysubstituted or mixed substituted by halogen or alkoxy;
- 20 R^{124} denotes halogen, hydroxyl, a straight-chained or branched alkyl, alkoxy, acyloxy or alkyloxycarbonyl group with 1-6 C- atoms, which can optionally be mono- or polysubstituted by halogen, NO_2 , $-OR^{121}$, $-COR^{121}$, $-CO_2 R^{121}$, $-OCO_2 R^{121}$, $-CN$, $-CONR^{121} OR^{122}$, $-CONR^{121} R^{122}$, $-SR^{121}$, $-S(O)R^{121}$, $-S(O)_2 R^{121}$, $-NR^{121} R^{122}$, $-NHC(O)R^{121}$, $-NHS(O)_2 R^{121}$, or a polyfluoroalkyl group;
- 25 R^{121} and R^{122} , independently from one another, denote hydrogen, alkyl, aralkyl or aryl; and
- m denotes a whole number from 0 to 2;
- 30 and the pharmaceutically-acceptable salts thereof.

[000137] Compounds that are useful as Cox-2 selective inhibitors of the present invention include phenyl heterocycles that are described in U.S.

Patent Nos. 5,474,995 and 6,239,173. Such phenyl heterocyclic compounds have the formula shown below in formula **XXIV**:



or pharmaceutically acceptable salts thereof wherein:

5 $X^{17}-Y^1-Z^7$ is selected from the group consisting of:

- (a) $-\text{CH}_2 \text{ CH}_2 \text{ CH}_2 -$,
- (b) $-\text{C}(\text{O})\text{CH}_2 \text{ CH}_2 -$,
- (c) $-\text{CH}_2 \text{ CH}_2 \text{ C}(\text{O})-$,
- (d) $-\text{CR}^{129} (\text{R}^{129'})-\text{O}-\text{C}(\text{O})-$,
- 10 (e) $-\text{C}(\text{O})-\text{O}-\text{CR}^{129} (\text{R}^{129'})-$,
- (f) $-\text{CH}_2 -\text{NR}^{127} -\text{CH}_2 -$,
- (g) $-\text{CR}^{129} (\text{R}^{129'})-\text{NR}^{127} -\text{C}(\text{O})-$,
- (h) $-\text{CR}^{128}=\text{CR}^{128'}-\text{S}-$,
- (i) $-\text{S}-\text{CR}^{128}=\text{CR}^{128'}-$,
- 15 (j) $-\text{S}-\text{N}=\text{CH}-$,
- (k) $-\text{CH}=\text{N}-\text{S}-$,
- (l) $-\text{N}=\text{CR}^{128} -\text{O}-$,
- (m) $-\text{O}-\text{CR}^{128}=\text{N}-$,
- (n) $-\text{N}=\text{CR}^{128} -\text{NH}-$,
- 20 (o) $-\text{N}=\text{CR}^{128} -\text{S}-$, and
- (p) $-\text{S}-\text{CR}^{128}=\text{N}-$,
- (q) $-\text{C}(\text{O})-\text{NR}^{127} -\text{CR}^{129} (\text{R}^{129'})-$,

(r) $\text{---R}^{127}\text{N---CH=CH---}$ provided R^{122} is not $\text{---S(O)}_2\text{CH}_3$,

(s) $\text{---CH=CH---NR}^{127}\text{---}$ provided R^{125} is not $\text{---S(O)}_2\text{CH}_3$;

when side b is a double bond, and sides a and c are single bonds; and

$\text{X}^{17}\text{---Y}^1\text{---Z}^7$ is selected from the group consisting of:

5 (a) =CH---O---CH= , and

(b) $\text{=CH---NR}^{127}\text{---CH=}$,

(c) =N---S---CH= ,

(d) =CH---S---N= ,

(e) =N---O---CH= ,

10 (f) =CH---O---N= ,

(g) =N---S---N= ,

(h) =N---O---N= ,

when sides a and c are double bonds and side b is a single bond;

R^{125} is selected from the group consisting of:

15 (a) $\text{S(O)}_2\text{CH}_3$,

(b) $\text{S(O)}_2\text{NH}_2$,

(c) $\text{S(O)}_2\text{NHC(O)CF}_3$,

(d) S(O)(NH)CH_3 ,

(e) S(O)(NH)NH_2 ,

20 (f) $\text{S(O)(NH)NHC(O)CF}_3$,

(g) $\text{P(O)(CH}_3\text{)OH}$, and

(h) $\text{P(O)(CH}_3\text{)NH}_2$;

R^{126} is selected from the group consisting of

(a) $\text{C}_1\text{---C}_6$ alkyl,

25 (b) C_3 , C_4 , C_5 , C_6 , and C_7 , cycloalkyl,

(c) mono-, di- or tri-substituted phenyl or naphthyl, wherein the substituent is selected from the group consisting of:

(1) hydrogen,

(2) halo,

30 (3) $\text{C}_1\text{---C}_6$ alkoxy,

(4) $\text{C}_1\text{---C}_6$ alkylthio,

(5) CN,

- (6) CF_3 ,
 (7) $\text{C}_1\text{--C}_6$ alkyl,
 (8) N_3 ,
 (9) $\text{--CO}_2\text{H}$,
 5 (10) $\text{--CO}_2\text{--C}_1\text{--C}_4$ alkyl,
 (11) $\text{--C(R}^{129}\text{)(R}^{130}\text{)--OH}$,
 (12) $\text{--C(R}^{129}\text{)(R}^{130}\text{)--O--C}_1\text{--C}_4$ alkyl, and
 (13) $\text{--C}_1\text{--C}_6$ alkyl- $\text{CO}_2\text{--R}^{129}$;

(d) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a
 10 monocyclic aromatic ring of 5 atoms, said ring having one hetero atom
 which is S, O, or N, and optionally 1, 2, or 3 additionally N atoms; or the
 heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero
 atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said
 substituents are selected from the group consisting of:

- 15 (1) hydrogen,
 (2) halo, including fluoro, chloro, bromo and iodo,
 (3) $\text{C}_1\text{--C}_6$ alkyl,
 (4) $\text{C}_1\text{--C}_6$ alkoxy,
 (5) $\text{C}_1\text{--C}_6$ alkylthio,
 20 (6) CN ,
 (7) CF_3 ,
 (8) N_3 ,
 (9) $\text{--C(R}^{129}\text{)(R}^{130}\text{)--OH}$, and
 (10) $\text{--C(R}^{129}\text{)(R}^{130}\text{)--O--C}_1\text{--C}_4$ alkyl;

25 (e) benzoheteroaryl which includes the benzo fused analogs of (d);
 R^{127} is selected from the group consisting of:

- (a) hydrogen,
 (b) CF_3 ,
 (c) CN
 30 (d) $\text{C}_1\text{--C}_6$ alkyl,
 (e) hydroxyl $\text{C}_1\text{--C}_6$ alkyl,
 (f) $\text{--C(O)--C}_1\text{--C}_6$ alkyl,

(g) optionally substituted:

- (1) $-\text{C}_1-\text{C}_5$ alkyl- Q^5 ,
- (2) $-\text{C}_1-\text{C}_5$ alkyl-O- $-\text{C}_1-\text{C}_3$ alkyl- Q^5 ,
- (3) $-\text{C}_1-\text{C}_3$ alkyl-S- $-\text{C}_1-\text{C}_3$ alkyl- Q^5 ,
- (4) $-\text{C}_1-\text{C}_5$ alkyl-O- Q^5 , or
- (5) $-\text{C}_1-\text{C}_5$ alkyl-S- Q^5 ,

5

wherein the substituent resides on the alkyl and the substituent is C_1-C_3 alkyl;

(h) $-\text{Q}^5$;

10

R^{128} and $\text{R}^{128'}$ are each independently selected from the group consisting of:

- (a) hydrogen,
- (b) CF_3 ,
- (c) CN ,
- (d) C_1-C_6 alkyl,
- (e) $-\text{Q}^5$,
- (f) $-\text{O}-\text{Q}^5$,
- (g) $-\text{S}-\text{Q}^5$, and

15

(h) optionally substituted:

20

- (1) $-\text{C}_1-\text{C}_5$ alkyl- Q^5 ,
- (2) $-\text{O}-\text{C}_1-\text{C}_5$ alkyl- Q^5 ,
- (3) $-\text{S}-\text{C}_1-\text{C}_5$ alkyl- Q^5 ,
- (4) $-\text{C}_1-\text{C}_3$ alkyl-O- $-\text{C}_1-\text{C}_3$ alkyl- Q^5 ,
- (5) $-\text{C}_1-\text{C}_3$ alkyl-S- $-\text{C}_1-\text{C}_3$ alkyl- Q^5 ,
- (6) $-\text{C}_1-\text{C}_5$ alkyl-O- Q^5 ,
- (7) $-\text{C}_1-\text{C}_5$ alkyl-S- Q^5 ,

25

wherein the substituent resides on the alkyl and the substituent is C_1-C_3 alkyl, and

R^{129} , $\text{R}^{129'}$, R^{130} , R^{131} and R^{132} are each independently selected from the group consisting of:

30

- (a) hydrogen,
- (b) C_1-C_6 alkyl;

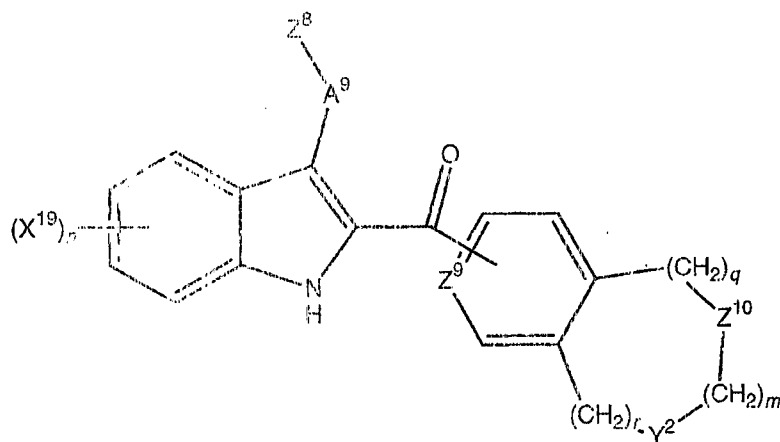
or R^{129} and R^{130} or R^{131} and R^{132} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

Q^5 is CO_2H , $CO_2-C_1-C_4$ alkyl, tetrazolyl-5-yl, $C(R^{131})(R^{132})(OH)$, or $C(R^{131})(R^{132})(O-C_1-C_4$ alkyl);

provided that when $X-Y-Z$ is $-S-CR^{128}=CR^{128'}$, then R^{128} and $R^{128'}$ are other than CF_3 .

[000138] An exemplary phenyl heterocycle that is disclosed in U.S. Patent No. 6,239,173 is 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(2H)-furanone.

[000139] Bicycliccarbonyl indole compounds such as those described in U.S. Patent No. 6,303,628 are useful as Cox-2 selective inhibitors of the present invention. Such bicycliccarbonyl indole compounds have the formula shown below in formula **XXV**:



XXV

or the pharmaceutically acceptable salts thereof wherein:

A^9 is C_1-C_6 alkylene or $-NR^{133}-$;

Z^8 is $C(=O)R^{134}$, or SO_2R^{135} ;

Z^9 is CH or N ;

Z^{10} and Y^2 are independently selected from $-CH_2-$, O , S and $-N-R^{133}$;

m is 1, 2 or 3;

q and r are independently 0, 1 or 2;

X^{18} is independently selected from halogen, C_1-C_4 alkyl, halo-substituted C_1-C_4 alkyl, hydroxyl, C_1-C_4 alkoxy, halo-substituted C_1-C_4 alkoxy, C_1-C_4 alkylthio, nitro, amino, mono- or di- $(C_1-C_4$ alkyl)amino and cyano;
 n is 0, 1, 2, 3 or 4;

5 L^3 is oxygen or sulfur;

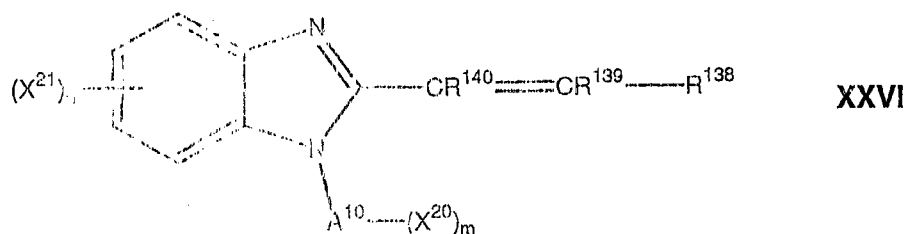
R^{133} is hydrogen or C_1-C_4 alkyl;

R^{134} is hydroxyl, C_1-C_6 alkyl, halo-substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, halo-substituted C_1-C_6 alkoxy, C_3-C_7 cycloalkoxy, C_1-C_4 alkyl(C_3-C_7 cycloalkoxy) $-NR^{136}R^{137}$, C_1-C_4 alkylphenyl-O— or phenyl-O—, said
 10 phenyl being optionally substituted with one to five substituents independently selected from halogen, C_1-C_4 alkyl, hydroxyl, C_1-C_4 alkoxy and nitro;

R^{135} is C_1-C_6 alkyl or halo-substituted C_1-C_6 alkyl; and

R^{136} and R^{137} are independently selected from hydrogen, C_{1-6} alkyl and
 15 halo-substituted C_1-C_6 alkyl.

[000140] Materials that can serve as a Cox-2 selective inhibitor of the present invention include benzimidazole compounds that are described in U.S. Patent No. 6,310,079. Such benzimidazole compounds have the formula shown below in formula XXVI:



20

or a pharmaceutically acceptable salt thereof, wherein:

A^{10} is heteroaryl selected from

a 5-membered monocyclic aromatic ring having one hetero atom selected
 25 from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom, or

a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and said heteroaryl being connected to the nitrogen atom on the benzimidazole through a carbon atom on the heteroaryl ring;

- 5 X^{20} is independently selected from halo, C_1-C_4 alkyl, hydroxyl, C_1-C_4 alkoxy, halo-substituted C_1-C_4 alkyl, hydroxyl-substituted C_1-C_4 alkyl, (C_1-C_4 alkoxy)(C_1-C_4 alkyl), halo-substituted C_1-C_4 alkoxy, amino, N-(C_1-C_4 alkyl)amino, N,N-di(C_1-C_4 alkyl)amino, [N-(C_1-C_4 alkyl)amino] C_1-C_4 alkyl, [N,N-di(C_1-C_4 alkyl)amino] C_1-C_4 alkyl, N-(C_1-C_4 alkanoyl)amino, N-(C_1-C_4 alkyl)(C_1-C_4 alkanoyl)amino, N-[(C_1-C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1-C_4 alkyl)sulfonyl]amino, C_1-C_4 alkanoyl, carboxy, (C_1-C_4 alkoxy)carbonyl, carbamoyl, [N-(C_1-C_4 alkyl)amino]carbonyl, [N,N-di(C_1-C_4 alkyl)amino]carbonyl, cyano, nitro, mercapto, (C_1-C_4 alkyl)thio, (C_1-C_4 alkyl)sulfinyl, (C_1-C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1-C_4 alkyl)amino]sulfonyl and [N,N-di(C_1-C_4 alkyl)amino]sulfonyl;
- 10 X^{21} is independently selected from halo, C_1-C_4 alkyl, hydroxyl, C_1-C_4 alkoxy, halo-substituted C_1-C_4 alkyl, hydroxyl-substituted C_1-C_4 alkyl, (C_1-C_4 alkoxy)(C_1-C_4 alkyl), halo-substituted C_1-C_4 alkoxy, amino, N-(C_1-C_4 alkyl)amino, N,N-di(C_1-C_4 alkyl)amino, [N-(C_1-C_4 alkyl)amino] C_1-C_4 alkyl, [N,N-di(C_1-C_4 alkyl)amino] C_1-C_4 alkyl, N-(C_1-C_4 alkanoyl)amino, N-(C_1-C_4 alkyl)(C_1-C_4 alkanoyl)amino, N-[(C_1-C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1-C_4 alkyl)sulfonyl]amino, C_1-C_4 alkanoyl, carboxy, (C_1-C_4 alkoxy)hydroxyl, carbamoyl, [N-(C_1-C_4 alkyl)amino]carbonyl, [N,N-di(C_1-C_4 alkyl)amino]carbonyl, N-carbamoylamino, cyano, nitro, mercapto, (C_1-C_4 alkyl)thio, (C_1-C_4 alkyl)sulfinyl, (C_1-C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1-C_4 alkyl)amino]sulfonyl and [N,N-di(C_1-C_4 alkyl)amino]sulfonyl;
- 15 R^{138} is selected from hydroxyl, straight or branched C_1-C_4 alkyl optionally substituted with one to three substituents; wherein said substituents are independently selected from
- 20
- 25
- 30

- halo, hydroxyl, C_1-C_4 alkoxy, amino, $N-(C_1-C_4 \text{ alkyl})$ amino and N, N -
 $di(C_1-C_4 \text{ alkyl})$ amino;
 C_3-C_3 cycloalkyl optionally substituted with one to three substituent(s)
 wherein said substituents are independently selected from halo, C_1-C_4 alkyl,
 hydroxyl, C_1-C_4 alkoxy, amino, $N-(C_1-C_4 \text{ alkyl})$ amino and N, N - $di(C_1-C_4$
 5 $alkyl)$ amino;
 C_4-C_4 cycloalkenyl optionally substituted with one to three substituent(s)
 wherein said substituents are independently selected from halo, C_1-C_4
 alkyl, hydroxyl, C_1-C_4 alkoxy, amino, $N-(C_1-C_4 \text{ alkyl})$ amino and N, N -
 10 $di(C_1-C_4 \text{ alkyl})$ amino;
 phenyl optionally substituted with one to three substituent(s) wherein said
 substituents are independently selected from halo, C_1-C_4 alkyl, hydroxyl,
 C_1-C_4 alkoxy, halo-substituted C_1-C_4 alkyl, hydroxyl-substituted C_1-C_4
 alkyl, $(C_1-C_4 \text{ alkoxy})C_1-C_4$ alkyl, halo-substituted C_1-C_4 alkoxy, amino,
 15 $N-(C_1-C_4 \text{ alkyl})$ amino, N, N - $di(C_1-C_4 \text{ alkyl})$ amino, $[N-(C_1-C_4$
 $alkyl)]$ amino, C_1-C_4 alkyl, $[N, N$ - $di(C_1-C_4 \text{ alkyl})$ amino] C_1-C_4 alkyl, $N-(C_1-C_4$
 $alkoxy)$ amino, $N-(C_1-C_4 \text{ alkyl})(C_1-C_4 \text{ alkanoyl})$ amino, $N-[(C_1-C_4$
 $alkyl)carbonyl]$ amino, $N-[(\text{halo-substituted } C_1-C_4 \text{ alkyl})\text{sulfonyl}]$ amino, C_1-C_4
 $alkanoyl$, carboxyl, $(C_1-C_4 \text{ alkoxy})$ carbonyl, carbomoyl, $[N-(C_1-C_4$
 20 $alkyl)amino]carbonyl$, N, N - $di(C_1-C_4 \text{ alkyl})$ amino]carbonyl, cyano, nitro,
 mercapto, $(C_1-C_4 \text{ alkyl})$ thio, $(C_1-C_4 \text{ alkyl})$ sulfinyl, $(C_1-C_4 \text{ alkyl})$ sulfonyl,
 amino, thio, $N-(C_1-C_4 \text{ alkyl})$ amino]sulfonyl and $[N, N$ - $di(C_1-C_4$
 $alkyl)amino]sulfonyl$; and
 heterocycloalkyl, and
 25 a 5-membered monocyclic aromatic ring having one hetero atom selected
 from S and O and optionally containing one to three N atom(s) in
 addition to said hetero atom; or a 6-membered monocyclic aromatic ring
 having one hetero atom and optionally containing one to four N atom(s) in
 addition to said hetero atom;
 30 said hetero atom optionally substituted with one to three substituent(s)
 selected from halo,
 R^{136} and R^{137} are independently selected from:

hydroxyl;

halo;

 C_1-C_4 alkyl;

phenyl optionally substituted with one to three substituent(s) wherein said substituent(s) is/are independently selected from halo, C_1-C_4 alkyl, hydroxyl, C_1-C_4 alkoxy, amino, N-(C_1-C_4 alkyl)amino and N, N-di(C_1-C_4 alkyl)amino;

or F^{12} and F^{13} can combine together with the carbon atom to which they are attached to form a cycloalkyl ring;

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000, 1001, 1002, 1003, 1004, 1005, 1006, 1007, 1008, 1009, 1010, 1011, 1012, 1013, 1014, 1015, 1016, 1017, 1018, 1019, 1020, 1021, 1022, 1023, 1024, 1025, 1026, 1027, 1028, 1029, 1030, 1031, 1032, 1033, 1034, 1035, 1036, 1037, 1038, 1039, 1040, 1041, 1042, 1043, 1044, 1045, 1046, 1047, 1048, 1049, 1050, 1051, 1052, 1053, 1054, 1055, 1056, 1057, 1058, 1059, 1060, 1061, 1062, 1063, 1064, 1065, 1066, 1067, 1068, 1069, 1070, 1071, 1072, 1073, 1074, 1075, 1076, 1077, 1078, 1079, 1080, 1081, 1082, 1083, 1084, 1085, 1086, 1087, 1088, 1089, 1090, 1091, 1092, 1093, 1094, 1095, 1096, 1097, 1098, 1099, 1100, 1101, 1102, 1103, 1104, 1105, 1106, 1107, 1108, 1109, 1110, 1111, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1121, 1122, 1123, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1170, 1171, 1172, 1173, 1174, 1175, 1176, 1177, 1178, 1179, 1180, 1181, 1182, 1183, 1184, 1185, 1186, 1187, 1188, 1189, 1190, 1191, 1192, 1193, 1194, 1195, 1196, 1197, 1198, 1199, 1200, 1201, 1202, 1203, 1204, 1205, 1206, 1207, 1208, 1209, 1210, 1211, 1212, 1213, 1214, 1215, 1216, 1217, 1218, 1219, 1220, 1221, 1222, 1223, 1224, 1225, 1226, 1227, 1228, 1229, 1230, 1231, 1232, 1233, 1234, 1235, 1236, 1237, 1238, 1239, 1240, 1241, 1242, 1243, 1244, 1245, 1246, 1247, 1248, 1249, 1250, 1251, 1252, 1253, 1254, 1255, 1256, 1257, 1258, 1259, 1260, 1261, 1262, 1263, 1264, 1265, 1266, 1267, 1268, 1269, 1270, 1271, 1272, 1273, 1274, 1275, 1276, 1277, 1278, 1279, 1280, 1281, 1282, 1283, 1284, 1285, 1286, 1287, 1288, 1289, 1290, 1291, 1292, 1293, 1294, 1295, 1296, 1297, 1298, 1299, 1300, 1301, 1302, 1303, 1304, 1305, 1306, 1307, 1308, 1309, 1310, 1311, 1312, 1313, 1314, 1315, 1316, 1317, 1318, 1319, 1320, 1321, 1322, 1323, 1324, 1325, 1326, 1327, 1328, 1329, 1330, 1331, 1332, 1333, 1334, 1335, 1336, 1337, 1338, 1339, 1340, 1341, 1342, 1343, 1344, 1345, 1346, 1347, 1348, 1349, 1350, 1351, 1352, 1353, 1354, 1355, 1356, 1357, 1358, 1359, 1360, 1361, 1362, 1363, 1364, 1365, 1366, 1367, 1368, 1369, 1370, 1371, 1372, 1373, 1374, 1375, 1376, 1377, 1378, 1379, 1380, 1381, 1382, 1383, 1384, 1385, 1386, 1387, 1388, 1389, 1390, 1391, 1392, 1393, 1394, 1395, 1396, 1397, 1398, 1399, 1400, 1401, 1402, 1403, 1404, 1405, 1406, 1407, 1408, 1409, 1410, 1411, 1412, 1413, 1414, 1415, 1416, 1417, 1418, 1419, 1420, 1421, 1422, 1423, 1424, 1425, 1426, 1427, 1428, 1429, 1430, 1431, 1432, 1433, 1434, 1435, 1436, 1437, 1438, 1439, 1440, 1441, 1442, 1443, 1444, 1445, 1446, 1447, 1448, 1449, 1450, 1451, 1452, 1453, 1454, 1455, 1456, 1457, 1458, 1459, 1460, 1461, 1462, 1463, 1464, 1465, 1466, 1467, 1468, 1469, 1470, 1471, 1472, 1473, 1474, 1475, 1476, 1477, 1478, 1479, 1480, 1481, 1482, 1483, 1484, 1485, 1486, 1487, 1488, 1489, 1490, 1491, 1492, 1493, 1494, 1495, 1496, 1497, 1498, 1499, 1500, 1501, 1502, 1503, 1504, 1505, 1506, 1507, 1508, 1509, 1510, 1511, 1512, 1513, 1514, 1515, 1516, 1517, 1518, 1519, 1520, 1521, 1522, 1523, 1524, 1525, 1526, 1527, 1528, 1529, 1530, 1531, 1532, 1533, 1534, 1535, 1536, 1537, 1538, 1539, 1540, 1541, 1542, 1543, 1544, 1545, 1546, 1547, 1548, 1549, 1550, 1551, 1552, 1553, 1554, 1555, 1556, 1557, 1558, 1559, 1560, 1561, 1562, 1563, 1564, 1565, 1566, 1567, 1568, 1569, 1570, 1571, 1572, 1573, 1574, 1575, 1576, 1577, 1578, 1579, 1580, 1581, 1582, 1583, 1584, 1585, 1586, 1587, 1588, 1589, 1590, 1591, 1592, 1593, 1594, 1595, 1596, 1597, 1598, 1599, 1600, 1601, 1602, 1603, 1604, 1605, 1606, 1607, 1608, 1609, 1610, 1611, 1612, 1613, 1614, 1615, 1616, 1617, 1618, 1619, 1620, 1621, 1622, 1623, 1624, 1625, 1626, 1627, 1628, 1629, 1630, 1631, 1632, 1633, 1634, 1635, 1636, 1637, 1638, 1639, 1640, 1641, 1642, 1643, 1644, 1645, 1646, 1647, 1648, 1649, 1650, 1651, 1652, 1653, 1654, 1655, 1656, 1657, 1658, 1659, 1660, 1661, 1662, 1663, 1664, 1665, 1666, 1667, 1668, 1669, 1670, 1671, 1672, 1673, 1674, 1675, 1676, 1677, 1678, 1679, 1680, 1681, 1682, 1683, 1684, 1685, 1686, 1687, 1688, 1689, 1690, 1691, 1692, 1693, 1694, 1695, 1696, 1697, 1698, 1699, 1700, 1701, 1702, 1703, 1704, 1705, 1706, 1707, 1708, 1709, 1710, 1711, 1712, 1713, 1714, 1715, 1716, 1717, 1718, 1719, 1720, 1721, 1722, 1723, 1724, 1725, 1726, 1727, 1728, 1729, 1730, 1731, 1732, 1733, 1734, 1735, 1736, 1737, 1738, 1739, 1740, 1741, 1742, 1743, 1744, 1745, 1746, 1747, 1748, 1749, 1750, 1751, 1752, 1753, 1754, 1755, 1756, 1757, 1758, 1759, 1760, 1761, 1762, 1763, 1764, 1765, 1766, 1767, 1768, 1769, 1770, 1771, 1772, 1773, 1774, 1775, 1776, 1777, 1778, 1779, 1780, 1781, 1782, 1783, 1784, 1785, 1786, 1787, 1788, 1789, 1790, 1791, 1792, 1793, 1794, 1795, 1796, 1797, 1798, 1799, 1800, 1801, 1802, 1803, 1804, 1805, 1806, 1807, 1808, 1809, 1810, 1811, 1812, 1813, 1814, 1815, 1816, 1817, 1818, 1819, 1820, 1821, 1822, 1823, 1824, 1825, 1826, 1827, 1828, 1829, 1830, 1831, 1832, 1833, 1834, 1835, 1836, 1837, 1838, 1839, 1840, 1841, 1842, 1843, 1844, 1845, 1846, 1847, 1848, 1849, 1850, 1851, 1852, 1853, 1854, 1855, 1856, 1857, 1858, 1859, 1860, 1861, 1862, 1863, 1864, 1865, 1866, 1867, 1868, 1869, 1870, 1871, 1872, 1873, 1874, 1875, 1876, 1877, 1878, 1879, 1880, 1881, 1882, 1883, 1884, 1885, 1886, 1887, 1888, 1889, 1890, 1891, 1892, 1893, 1894, 1895, 1896, 1897, 1898, 1899, 1900, 1901, 1902, 1903, 1904, 1905, 1906, 1907, 1908, 1909, 1910, 1911, 1912, 1913, 1914, 1915, 1916, 1917, 1918, 1919, 1920, 1921, 1922, 1923, 1924, 1925, 1926, 1927, 1928, 1929, 1930, 1931, 1932, 1933, 1934, 1935, 1936, 1937, 1938, 1939, 1940, 1941, 1942, 1943, 1944, 1945, 1946, 1947, 1948, 1949, 1950, 1951, 1952, 1953, 1954, 1955, 1956, 1957, 1958, 1959, 1960, 1961, 1962, 1963, 1964, 1965, 1966, 1967, 1968, 1969, 1970, 1971, 1972, 1973, 1974, 1975, 1976, 1977, 1978, 1979, 1980, 1981, 1982, 1983, 1984, 1985, 1986, 1987, 1988, 1989, 1990, 1991, 1992, 1993, 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175

(c) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with one or two substituents independently selected from:

5 (c1) halo, C₁-C₄ alkyl, halosubstituted C₁-C₄ alkyl, hydroxyl, C₁-C₄ alkoxy, halosubstituted C₁-C₄ alkoxy, S(O)_m R¹⁴³, SO₂ NH₂, SO₂ N(C₁-C₄ alkyl)₂, amino, mono- or di-(C₁-C₄ alkyl)amino, NHSO₂ R¹⁴³, carbonyl, R¹⁴³, CO₂ H, CO₂ (C₁-C₄ alkyl), C₁-C₄ alkyl-OH, C₁-C₄ alkyl-OR¹⁴³, C₁-C₄ alkyl-OC(=O)H(C₁-C₄ alkyl), CON(C₁-C₄ alkyl)₂ and —
10 (c2) a heteroaryl group (being optionally substituted with one or two substituents independently selected from halo, C₁-C₄ alkyl, CF₃, hydroxyl, OR¹⁴³, S(O)_m R¹⁴³, amino, mono- or di-(C₁-C₄ alkyl)amino and CON),

(d) a monocyclic aromatic group of 5 atoms, said aromatic group having one heteroatom selected from O, S and N and optionally containing up to three additional substituents to said heteroatom, and said aromatic group
15 being substituted with one or three substituents independently selected from

(d1) halo, C₁-C₄ alkyl, halosubstituted C₁-C₄ alkyl, hydroxyl, C₁-C₄ alkoxy, halosubstituted C₁-C₄ alkoxy, C₁-C₄ alkyl-OH, S(O)_m R¹⁴³, SO₂ NH₂, SO₂ N(C₁-C₄ alkyl)₂, amino, mono- or di-(C₁-C₄ alkyl)amino, NHOR¹⁴³, NHCO(OR¹⁴³), CN, CO₂ H, CO₂ (C₁-C₄ alkyl), C₁-C₄ alkyl-OR¹⁴³, CONH₂, CONH(C₁-C₄ alkyl), CON(C₁-C₄ alkyl)₂,
20 (d2) a heteroaryl group (being optionally substituted with one or two substituents independently selected from halo, CF₃, C₁-C₄ alkyl, hydroxyl, C₁-C₄ alkoxy, OR¹⁴³, S(O)_m R¹⁴³, SO₂ CH₃, SO₂ NH₂, amino, C₁-4 alkylamino and CON),

(e) a monocyclic aromatic group of 6 atoms, said aromatic group having one heteroatom selected from O, S and N and optionally containing up to three atoms in addition to said heteroatom, and said aromatic group being substituted with one or three substituents independently selected from the above group

(d-
30 R¹⁴³ and R¹⁴⁴ are each C₁-C₄ alkyl optionally substituted with a substituent selected independently from hydroxyl, OR¹⁴³, nitro, amino, mono- or di-(C₁-

$-C_4$ alkyl), $-C_1-C_4$ alkenyl, $-CO_2H$, $-CO_2(C_1-C_4 \text{ alkyl})$, $CONH_2$, $CONH(C_1-C_4 \text{ alkyl})$
and $OC(O)R^{142}$;

R^{142} is

(a) H or OH ;

5 (b) C_1-C_4 alkyl;

(c) C_1-C_4 alkenyl;

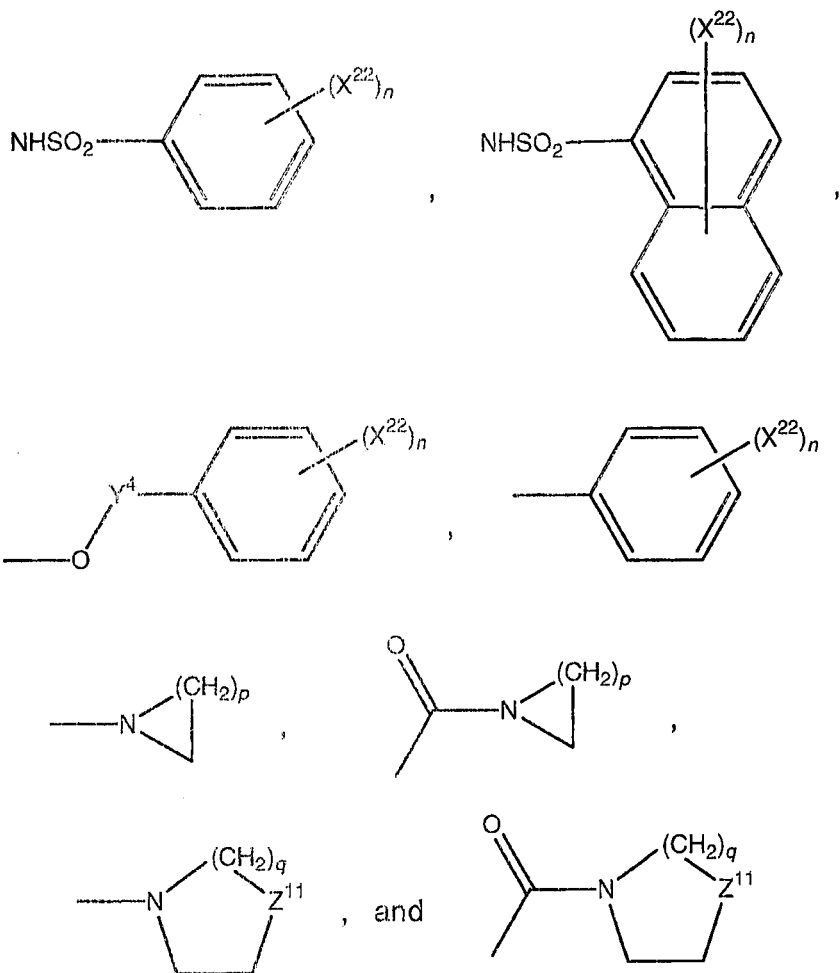
wherein R^{142} is not a phenyl group.

Each R^{142} is a C_1-C_{22} alkyl, said alkyl or alkenyl being
optionally substituted with up to four substituents independently
selected from

10

H , OH , OR^{143} , CO_2R^{143} , SO_2R^{143} , NO_2 , amino, mono- or di-
substituted amino, $-SO_2R^{143}$, $-CO_2H$, $-CO_2(C_1-C_4 \text{ alkyl})$, $CONH_2$,
 $CON(C_1-C_4 \text{ alkyl})_2$, $OC(O)R^{143}$, thienyl,
and any combination of the following formulas:

15



(c-2) C_1 – C_{22} alkyl or C_2 – C_{22} alkenyl, said alkyl or alkenyl being optionally substituted with five to forty-five halogen atoms,

(c-3) $-\text{Y}^5-\text{C}_3$ – C_7 cycloalkyl or $-\text{Y}^5-\text{C}_3$ – C_7 cycloalkenyl, said cycloalkyl or cycloalkenyl being optionally substituted with up to three substituent independently selected from:

(c-3-1) C_1 – C_4 alkyl, hydroxyl, OR^{143} , $\text{S(O)}_m \text{R}^{143}$, amino, mono- or di- (C_1 – C_4 alkyl)amino, CONH_2 , $\text{CONH}(\text{C}_1$ – C_4 alkyl) and $\text{CON}(\text{C}_1$ – C_4 alkyl) $_2$,

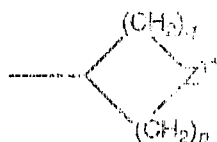
(c-4) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to seven (preferably up to seven) substituents independently selected from:

(c-4-1) halo, C_1-C_8 alkyl, C_1-C_4 alkyl-OH, hydroxyl, C_1-C_8 alkoxy, halosubstituted C_1-C_8 alkyl, halosubstituted C_1-C_8 alkoxy, CN, nitro, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 NH(C_1-C_4 \text{ alkyl})$, $SO_2 N(C_1-C_4 \text{ alkyl})_2$, amino, C_1-C_4 alkylamino, di- $(C_1-C_4 \text{ alkyl})$ amino, $CONH_2$, $CONH(C_1-C_4 \text{ alkyl})$, $CON(C_1-C_4 \text{ alkyl})_2$, $OC(O)R^{143}$, and phenyl optionally substituted with up to three substituents independently selected from halo, C_1-C_4 alkyl, hydroxyl, OCH_3 , CF_3 , OCF_3 , CN, nitro, amino, mono- or di- $(C_1-C_4 \text{ alkyl})$ amino, $CO_2 H$, $CO_2 (C_1-C_4 \text{ alkyl})$ and $CONH_2$,

(c-5) a monocyclic aromatic group as defined in (d) and (e) above, said aromatic group being optionally substituted with up to three substituents independently selected from:

(c-5-1) halo, C_1-C_8 alkyl, C_1-C_4 alkyl-OH, hydroxyl, C_1-C_8 alkoxy, CF_3 , OCF_3 , CN, nitro, $S(O)_m R^{143}$, amino, mono- or di- $(C_1-C_4 \text{ alkyl})$ amino, $CONH_2$, $CONH(C_1-C_4 \text{ alkyl})$, $CON(C_1-C_4 \text{ alkyl})_2$, $CO_2 H$ and $CO_2 (C_1-C_4 \text{ alkyl})$, and $-Y$ -phenyl, said phenyl being optionally substituted with up to three substituents independently selected halogen, C_1-C_4 alkyl, hydroxyl, C_1-C_4 alkoxy, CF_3 , OCF_3 , CN, nitro, $S(O)_m R^{143}$, amino, mono- or di- $(C_1-C_4 \text{ alkyl})$ amino, $CO_2 H$, $CO_2 (C_1-C_4 \text{ alkyl})$, $CONH_2$, $CONH(C_1-C_4 \text{ alkyl})$ and $CON(C_1-C_4 \text{ alkyl})_2$,

(c-6) a group of the following formula:



X^{22} is halo, C_1-C_4 alkyl, hydroxyl, C_1-C_4 alkoxy, halosubstituted C_1-C_4 alkoxy, $S(O)_m R^{143}$, amino, mono- or di- $(C_1-C_4 \text{ alkyl})$ amino, $NHSO_2 R^{143}$, nitro, halosubstituted C_1-C_4 alkyl, CN, $CO_2 H$, $CO_2 (C_1-C_4 \text{ alkyl})$, C_1-C_4 alkyl-OH, C_1-C_4 alkylOR¹⁴³, $CONH_2$, $CONH(C_1-C_4 \text{ alkyl})$ or $CON(C_1-C_4 \text{ alkyl})_2$;

R^{143} is C_1 – C_4 alkyl or halosubstituted C_1 – C_4 alkyl;

m is 0, 1 or 2; n is 0, 1, 2 or 3; p is 1, 2, 3, 4 or 5; q is 2 or 3;

Z^{11} is oxygen, sulfur or NR^{146} ; and

R^{144} is hydrogen, C_1 – C_6 alkyl, halosubstituted C_1 – C_4 alkyl or $-Y^5$ -

5 phenyl, said phenyl being optionally substituted with up to two substituents independently selected from halo, C_1 – C_4 alkyl, hydroxyl, C_1 – C_4 alkoxy, $S(O)_m R^{143}$, amino, mono- or di- $(C_1$ – C_4 alkyl)amino, CF_3 , OCF_3 , CN and nitro;

with the proviso that a group of formula $-Y^5-Q$ is not methyl or ethyl when

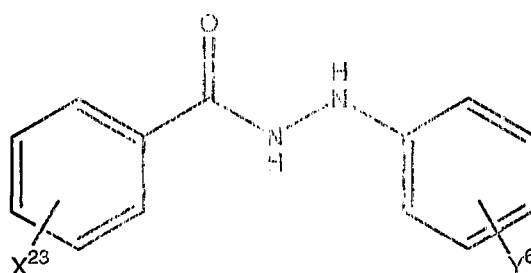
10 X^{22} is hydrogen,

L^4 is oxygen;

R^{141} is hydrogen; and

R^{142} is acetyl.

[000142] Aryl phenylhydrazides that are described in U.S. Patent No.
15 6,077,869 can serve as Cox-2 selective inhibitors of the present invention.
Such aryl phenylhydrazides have the formula shown below in formula
XXVIII:

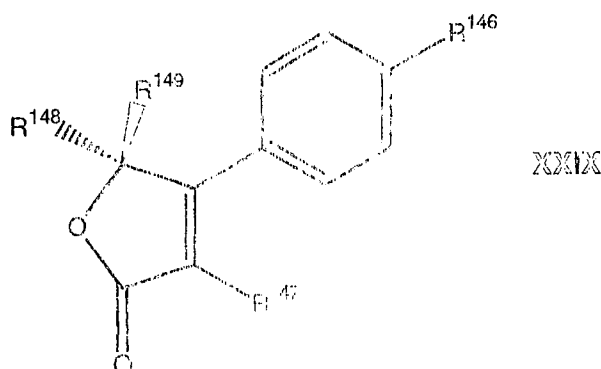


XXVIII

wherein:

20 X^{23} and Y^6 are selected from hydrogen, halogen, alkyl, nitro, amino, hydroxy, methoxy and methylsulfonyl;
or a pharmaceutically acceptable salt thereof.

[000143] Materials that can serve as a Cox-2 selective inhibitor of the
present invention include 2-aryloxy, 4-aryl furan-2-ones that are described
25 in U.S. Patent No. 6,140,515. Such 2-aryloxy, 4-aryl furan-2-ones have
the formula shown below in formula XXIX:



or a pharmaceutical salt thereof, wherein:

R^{146} is selected from the group consisting of SCH_3 , $-\text{S}(\text{O})_2 \text{CH}_3$ and $-\text{S}(\text{O})_2 \text{NH}_2$;

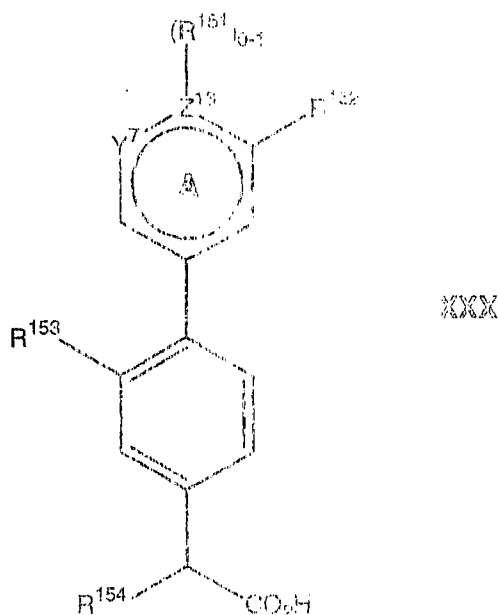
R^{147} is selected from the group consisting of OR^{150} , mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{150} is unsubstituted or mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{148} is H , C_1-C_4 alkyl optionally substituted with 1 to 3 groups of F, Cl or Br; and

R^{149} is H , C_1-C_4 alkyl optionally substituted with 1 to 3 groups of F, Cl or Br, with the proviso that R^{148} and R^{149} are not the same.

[000144] Materials that can serve as a Cox-2 selective inhibitor of the present invention include bisaryl compounds that are described in U.S. Patent No. 5,994,379. Such bisaryl compounds have the formula shown below in formula XXX:



or a pharmaceutically acceptable salt, ester or tautomer thereof, wherein:

Z^{13} is C or N;

when Z^{13} is N, R^{151} represents H or is absent, or is taken in conjunction with R^{152} as described below:

5

when Z^{13} is C, R^{151} represents H and R^{152} is a moiety which has the following characteristic:

(a) it is a linear chain of 3-4 atoms containing 0-2 double bonds, which can adopt an energetically stable transoid configuration and if a double bond is present, the bond is in the trans configuration,

10

(b) it is lipophilic except for the atom bonded directly to ring A, which is either lipophilic or non-lipophilic, and

(c) there exists an energetically stable configuration planar with ring A to within about 15 degrees;

15

or R^{151} and R^{152} are taken in combination and represent a 5- or 6-

membered aromatic or non-aromatic ring D fused to ring A, said ring D containing 0-3 heteroatoms selected from O, S and N;

said ring D being lipophilic except for the atoms attached directly to ring A, which are lipophilic or non-lipophilic, and said ring D having available an

energetically stable conformation planar with ring A to within about 15 degrees;

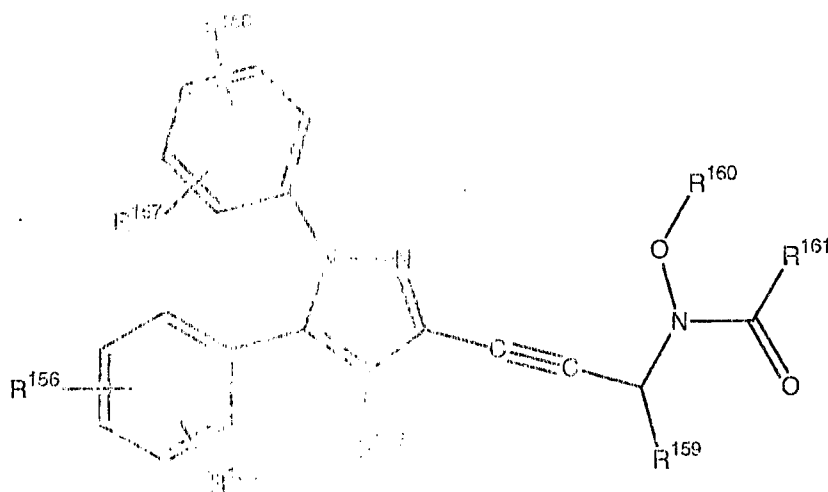
said ring D further being substituted with 1 R^a group selected from the group consisting of: C₁-C₂ alkyl, —OC₁-C₂ alkyl, —NHC₁-C₂ alkyl, —N(C₁-C₂ alkyl)₂, —O(C₁-C₂ alkyl), —S—C₁-C₂ alkyl and —C(S) C₁-C₂ alkyl;

Y⁷ represents H, OH or C—CC₁—C₃ alkyl, and when Z¹³ is N, Y⁷ can also represent a carbonyl group.

R^{153} represents H, Br, Cl or CH_3 and

R¹⁵⁴ represents 14 of 151

[000145] Compounds useful as Cox-2 selective inhibitors of the present invention include 1,5-diarylpyrzoles that are described in U.S. Patent No. 6,028,202. Such 1,5-diarylpyrzoles have the formula shown below in formula XXXI:

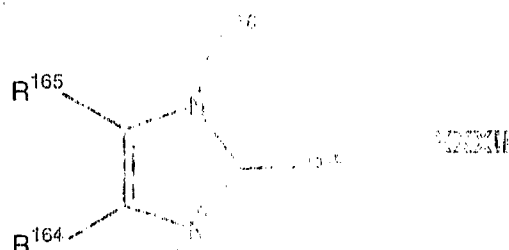


XXXI

wherein:

R¹⁵⁵, R¹⁵³, R¹⁵⁷, and R¹⁵⁶ are independently selected from the groups consisting of hydrogen, C₁-C₅ alkyl, C₁-C₅ alkoxy, phenyl, halo, hydroxyl, C₁-C₅ alkylsulfonyl, C₁-C₅ alkylthio, trihaloC₁-C₅ alkyl, amino, nitro and 2-quinolinecarboxyl.

- R^{159} is hydrogen, C_1-C_5 alkyl, trihalo C_1-C_5 alkyl, phenyl, substituted phenyl where the phenyl substituents are halogen, C_1-C_5 alkoxy, trihalo C_1-C_5 alkyl or nitro; or R^{159} is heteroaryl of 5-7 ring members where at least one of the ring members is nitrogen, sulfur or oxygen;
- 5 R^{160} is hydrogen, C_1-C_5 alkyl, phenyl, C_1-C_5 alkyl, substituted phenyl, C_1-C_5 alkyl where the phenyl substituents are halogen, C_1-C_5 alkoxy, trihalo C_1-C_5 alkyl or nitro; or R^{160} is C_1-C_5 alkoxy, carbonyl, phenoxy, carbonyl, substituted phenoxy, carbonyl where the phenyl substituents are halogen, C_1-C_5 alkoxy, trihalo C_1-C_5 alkyl or nitro;
- 10 R^{161} is C_1-C_{10} alkyl, phenyl, and C_1-C_{10} alkyl where the substituents are halogen, trihalo C_1-C_5 alkyl, C_1-C_5 alkoxy, carboxy, C_1-C_5 alkoxy, carbonyl, amino, C_1-C_5 alkylamino, di C_1-C_5 alkylamino, di C_1-C_5 alkylamino C_1-C_5 alkylamino, C_1-C_5 alkylamino C_1-C_5 alkylamino or a heterocycle containing one or more atoms where one more of the ring atoms is
- 15 nitrogen, oxygen or sulfur; where said heterocycle may be optionally substituted with C_1-C_5 alkyl; or R^{161} is phenyl, substituted phenyl (where the phenyl substituents are one or more of C_1-C_5 alkyl, halogen, C_1-C_5 alkoxy, trihalo C_1-C_5 alkyl or nitro), or R^{161} is heteroaryl having 5-7 ring atoms where one or more atoms are nitrogen, oxygen or sulfur, fused
- 20 heteroaryl where one or more 5-7 membered aromatic rings are fused to the heterocycle;
- R^{161} is $N(R^{162})R^{163}$ where R^{162} and R^{163} are independently selected from hydrogen and C_1-C_5 alkyl; or R^{161} and R^{163} may be taken together with the depicted nitrogen to form a heteroaryl ring of 5-7 ring members where one or more of the ring members are nitrogen, sulfur or oxygen where said heteroaryl ring may be optionally substituted with C_1-C_5 alkyl; R^{162} is
- 25 hydrogen, C_1-C_5 alkyl, amino, and halogen;
- and pharmaceutically acceptable salts thereof.
- [000136] The compounds may serve as a Cox-2 selective inhibitor of the present invention that are substituted imidazoles that are described in
- 30 U.S. Patent No. 6,300,100. Such 2-substituted imidazoles have the formula shown below, where XXXII:



wherein,

R¹⁶⁴ is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, or

5 substituted phenol

wherein the substituents are independently selected from one or members of the group consisting of: hydrogen, alkyl, halogen, nitro, trifluoromethyl and nitrile;

10 R¹⁶⁵ is phenyl, heteroaryl or aryl, in the heteroaryl contains 5 to 6 ring atoms

substituted benzene-4,4'-diyl

wherein the substituents are independently selected from one or more members of the group consisting of C₁–C₆ alkyl and halogen, or substituted thereon;

15 wherein the substituent is independently selected from one or members of the group consisting of C_1 - C_5 alkyl, halogen, nitro, trifluoromethyl and nitrile;

20 R^{166} is hydrogen, 2,2,2-trifluoroethyl, (ethoxymethyl), C_1-C_5 alkoxy carbonyl, aryloxy carbonyl, aryl C_1-C_5 alkoxy carbonyl, aryl C_1-C_5 alkyl, phthalimido, 2,2,2-trifluoroethyl, C_1-C_5 alkyl, diamino C_1-C_5 alkyl, succinimido C_1-C_5 alkyl, C_1-C_5 alkyl carbonyl, aryl carbonyl, C_1-C_5 alkyl carbonyl, C_1-C_5 alkoxy carbonyl, C_1-C_5 alkyl, heteroaryl C_1-C_5 alkyl where heteroaryl contains 5 to 6 ring atoms, or substituent R^{166} is a group.

wherein the substituents are independently selected from one or more members of the group consisting of C₁-C₅ alkyl, C₁-C₅ alkoxy, halogen, amino, C₁-C₅ alkylamino and C₁-C₅ alkylamino;

R¹⁶⁷ is (CH₂)_n-C(=O)-R¹⁶⁸, wherein:

5 A¹¹ is substituted with:

n is 0 or 1;

q is 0-5;

X²⁴ is selected from the group consisting of hydrogen, hydroxyl, halogen,

vinyl, ethynyl, C₁-C₅ alkyl, C₁-C₅ cycloalkyl, C₁-C₅ alkoxy, phenoxy,

10 phenyl, aryl, C₁-C₅ alkylamino, nitrile, phthalimido,

amido, phenylamino, C₁-C₅ alkylaminocarbonyl, phenylaminocarbonyl,

aryl(C₁-C₅ alkyl)thio, C₁-C₅ alkylthio, C₁-C₅ alkylsulfonyl,

phenylsulfonyl,

substituted sulfonyl,

15 wherein the substituent is selected from the group consisting of C₁-C₅ alkyl, phenyl, C₁-C₅ alkyl, thienyl, furanyl, and naphthyl;

substituted with:

wherein the substituents are independently selected from one or members of the group consisting of fluorine, bromine, chlorine and iodine,

20 substituted with:

wherein the substituents are independently selected from one or more members of the group consisting of fluorine, bromine, chlorine and iodine, substituted with:

wherein the substituents are selected from the group consisting of one or more C₁-C₅ alkyl, C₁-C₅ alkoxy, phthalimido and amino,

25 substituted with:

wherein the substituents are independently selected from one or more members of the group consisting of C₁-C₅ alkyl, halogen and C₁-C₅ alkoxy,

30 substituted with:

- wherein the phenyl substituents are independently selected from one or more members of the group consisting of C₁–C₅ alkyl, halogen and C₁–C₅ alkoxy,
substituted C₁–C₅ alkoxy,
- 5 wherein the alkyl substituent is selected from the group consisting of phthalimido and amino,
substituted aryl/C₁–C₅ alkyl,
wherein the alkyl substituent is hydroxyl,
substituted aryl/C₁–C₅ alkyl,
- 10 wherein the phenyl substituents are independently selected from one or more members of the group consisting of C₁–C₅ alkyl, halogen and C₁–C₅ alkoxy,
substituted amido,
wherein the carbonyl substituent is selected from the group consisting of
- 15 C₁–C₅ alkyl, phenyl, aryl/C₁–C₅ alkyl, thienyl, furanyl, and naphthyl,
substituted phenylcarbonyl,
wherein the phenyl substituents are independently selected from one or more members of the group consisting of C₁–C₅ alkyl, halogen and C₁–C₅ alkoxy,
substituted C₁–C₅ alkylthio
- 20 wherein the alkyl substituent is selected from the group consisting of hydroxyl and phthalimido,
substituted C₁–C₅ alkylsulfonyl,
wherein the alkyl substituent is selected from the group consisting of
- 25 hydroxyl and phthalimido,
substituted phenylsulfonyl,
wherein the phenyl substituents are independently selected from one or more members of the group consisting of bromine, fluorine, chlorine, C₁–C₅ alkoxy and trifluoromethyl,
- 30 with the proviso:

if A^{11} is sulfur and X^{24} is other than hydrogen, C_1-C_5 alkylaminocarbonyl, phenylaminocarbonyl, aryl(C_1-C_5 alkylaminocarbonyl, C_1-C_5 alkylsulfonyl or phenylsulfonyl, then q must be equal to or greater than 1;

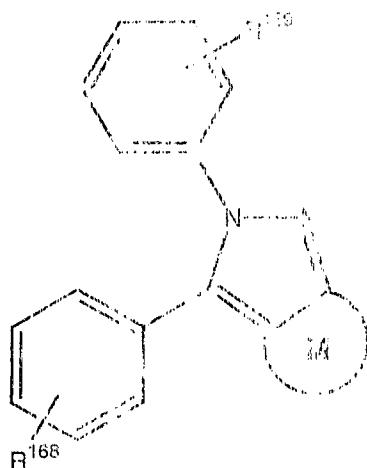
if A^{11} is sulfur and q is 1, then X^{24} cannot be C_1-C_2 alkyl;

5 if A^{11} is carbonyl and q is 0, then X^{24} cannot be vinyl, ethynyl, C_1-C_5 alkylaminocarbonyl, phenylaminocarbonyl, aryl(C_1-C_5 alkylaminocarbonyl, C_1-C_5 alkylsulfonyl or phenylsulfonyl;

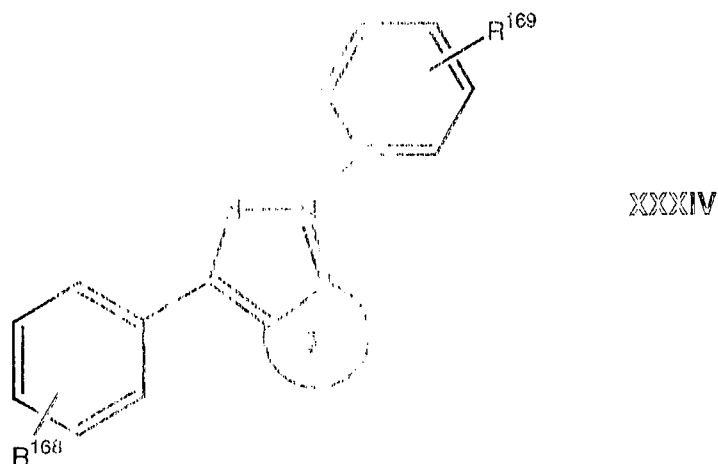
if A^{11} is carbonyl, q is 0 and X^{24} is H, then R^{166} is not 2-(trimethylsilyl)ethoxymethyl

10 if n is 0 and q is 0, then X^{24} cannot be hydrogen; and pharmaceutically acceptable salts thereof.

[000147] Materials that can serve as a Cox-2 selective inhibitor of the present invention include 1,3- and 2,3-diarylcycloalkano and cycloalkeno pyrazoles that are described in U.S. Patent No. 6,083,969. Such 1,3- and 2,3-diarylpyrazole compounds have the general formulas shown below in formulas XXXIII and XXXIV:



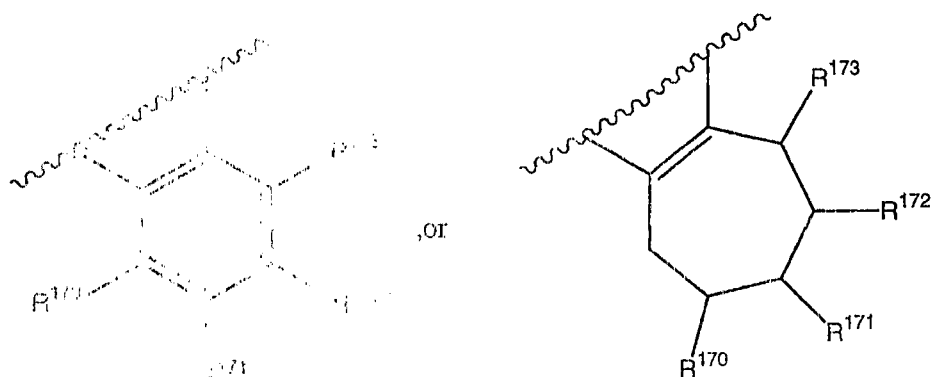
XXXIII



wherein:

R^{168} and R^{169} are independently selected from the group consisting of hydrogen, halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, nitro, amino, hydroxyl, trifluoro, $-S(C_1-C_6)alkyl$, $-SO(C_1-C_6)alkyl$ and $-SO_2(C_1-C_6)alkyl$; and

the fused moiety M is a group selected from the group consisting of an optionally substituted cyclohexyl and cycloheptyl group having the formulae:



wherein:

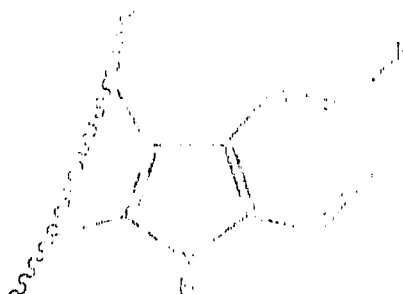
R^{170} is selected from the group consisting of hydrogen, halogen, hydroxyl and carbonyl;

or R^{170} and R^{171} taken together form a moiety selected from the group consisting of $-\text{OCOCH}_2-$, $-\text{ONH}(\text{CH}_3)\text{COCH}_2-$, $-\text{OCOCH=}$ and $-\text{O}-$;

5 R^{171} and R^{172} are independently selected from the group consisting of hydrogen, halogen, hydroxyl, carbonyl, amino, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, $-\text{OC(=O)-}$, $-\text{O}-$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{OSO}_2\text{NHCO}_2\text{CH}_3$, $-\text{OC(=O)CH}_2\text{CH}_3$, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{CH}_2\text{CO}_2\text{CH}_3$, $-\text{CH}_2\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CONH}(\text{CH}_3)$, $-\text{CH}_2\text{CO}_2\text{NHCH}_3$, $-\text{CHCHCO}_2\text{CH}_2\text{CH}_3$, $-\text{OCCN}(\text{CH}_3)\text{OH}$, $-\text{O}(\text{C}(\text{CH}_3)_2)_2$, $\text{di}(\text{C}_1-\text{C}_6)$ alkyl and $\text{di}(\text{C}_1-\text{C}_6)$ alkoxy;

10 R^{173} is selected from the group consisting of hydrogen, halogen, hydroxyl, carbonyl, amino, (C_1-C_6) alkyl, (C_1-C_6) alkoxy and optionally substituted carboxyphenyl, wherein substituents on the carboxyphenyl group are selected from the group consisting of halogen, hydroxyl, amino, (C_1-C_6) alkyl and (C_1-C_6) alkoxy;

15 or R^{172} and R^{173} taken together form a moiety selected from the group consisting of $-\text{O}-$ and $-\text{OCH}_2-$;



20 R^{174} is selected from the group consisting of hydrogen, OH, $-\text{OCOCH}_3$, $-\text{OH}(\text{CH}_3)$ and $-\text{O}(\text{CH}_3)_2$; and

R^{175} is selected from the group consisting of hydrogen, OH, $-\text{OCOCH}_3$, $-\text{COOH}$, (C_1-C_6) alkyl, $-\text{CONH}_2$ and $-\text{SO}_2\text{CH}_3$;

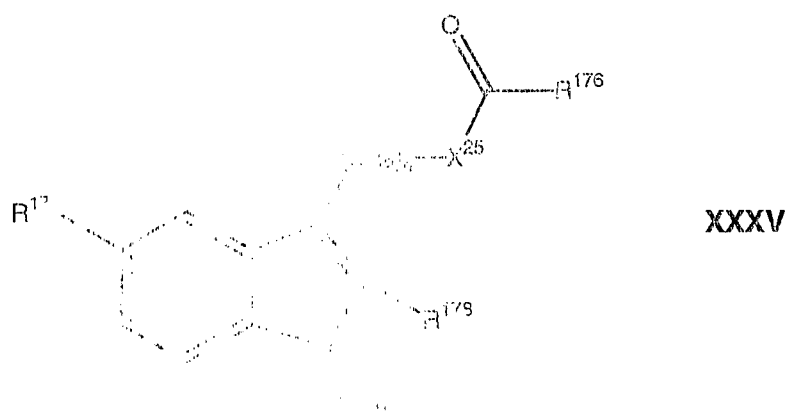
with the proviso that

if M is a group containing one or more R^{170} through R^{173} may not all be hydrogen;

25 and

pharmaceuticals, lyophilizates, salts, esters and pro-drug forms thereof.

[000148] Esters and esters of indolealkanols and novel amides derived from indolealkanols and are described in U.S. Patent No. 6,306,890 can serve as the selected inhibitors of the present invention. Such compounds have the general formula shown below in formula **XXXXV**:



where α

R¹⁷⁸: C₁-C₆ alkyl; C₄-C₈ branched alkyl, C₄-C₈ cycloalkyl, C₁-C₆ hydroxyalkyl, aryl substituted C₁-C₆ hydroxyalkyl, hydroxyl substituted C₄-C₈ aryl, primary or secondary C₁-C₆ alkylamino; primary, secondary or tertiary amine substituted C₁-C₆ alkylamino, primary, secondary or tertiary C₄-C₈ aryl amino, C₁-C₆ alkoxy carboxylic acid, branched C₁-C₆ alkylcarboxylic acid, C₄-C₈ aryl ester, branched C₁-C₆ alkylester, C₄-C₈ aryl, C₄-C₈ aryloxy carbonyl substituted alkylester, C₄-C₈ aryl substituted C₁-C₆ alkyl, C₄-C₈ aromatic heterocyclic ring fused with O, N or S in the ring, alkyl-substituted or aryl-substituted C₄-C₈ heterocyclic alkyl; or aryl with O, N or S in the ring; halo-phenyl groups thereof, where halo is chloro, bromo, fluoro or iodo.

20 R^{177} is C_1-C_6 alkyl, C_1-C_6 branched alkyl, C_4-C_8 cycloalkyl, C_4-C_8 aryl, C_4-C_8 cycloaryl, C_1-C_6 ether, C_1-C_6 ester, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 branched alkoxy, C_1-C_6 aryl, C_1-C_6 ester, or substituted versions thereof or R^{177} is halo where halo is fluorine, chlorine, bromine, or iodo;

$R^{1,8}$: H , CH_3 , CH_2CH_3 , $CH(CH_3)_2$, or C_4-C_6 branched alkyl;

R¹⁷ is C₁-C₃ alkyl, C₁-C₂ alkyl, C₄-C₈ aryl, C₄-C₈ heterocyclic alkyl or aryl with O, N or S in the ring, C₄-C₈ aryl-substituted C₁-C₆ alkyl, alkyl-substituted C₄-C₈ heterocyclic alkyl or aryl with O, N or S in the ring, C₄-C₈ heterocyclic alkyl or aryl with O, N or S in the ring, C₄-C₈ aryl, or alkyl-substituted C₄-C₈ aryl, or haloalkyl, where halo is chloro, bromo, or iodo;

n is 1.43, 1.44, 1.45, 1.46, 1.47, 1.48, 1.49, 1.50, 1.51, 1.52, 1.53, 1.54, 1.55, 1.56, 1.57, 1.58, 1.59, 1.60, 1.61, 1.62, 1.63, 1.64, 1.65, 1.66, 1.67, 1.68, 1.69, 1.70, 1.71, 1.72, 1.73, 1.74, 1.75, 1.76, 1.77, 1.78, 1.79, 1.80, 1.81, 1.82, 1.83, 1.84, 1.85, 1.86, 1.87, 1.88, 1.89, 1.90, 1.91, 1.92, 1.93, 1.94, 1.95, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09, 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24, 2.25, 2.26, 2.27, 2.28, 2.29, 2.30, 2.31, 2.32, 2.33, 2.34, 2.35, 2.36, 2.37, 2.38, 2.39, 2.40, 2.41, 2.42, 2.43, 2.44, 2.45, 2.46, 2.47, 2.48, 2.49, 2.50, 2.51, 2.52, 2.53, 2.54, 2.55, 2.56, 2.57, 2.58, 2.59, 2.60, 2.61, 2.62, 2.63, 2.64, 2.65, 2.66, 2.67, 2.68, 2.69, 2.70, 2.71, 2.72, 2.73, 2.74, 2.75, 2.76, 2.77, 2.78, 2.79, 2.80, 2.81, 2.82, 2.83, 2.84, 2.85, 2.86, 2.87, 2.88, 2.89, 2.90, 2.91, 2.92, 2.93, 2.94, 2.95, 2.96, 2.97, 2.98, 2.99, 3.00, 3.01, 3.02, 3.03, 3.04, 3.05, 3.06, 3.07, 3.08, 3.09, 3.10, 3.11, 3.12, 3.13, 3.14, 3.15, 3.16, 3.17, 3.18, 3.19, 3.20, 3.21, 3.22, 3.23, 3.24, 3.25, 3.26, 3.27, 3.28, 3.29, 3.30, 3.31, 3.32, 3.33, 3.34, 3.35, 3.36, 3.37, 3.38, 3.39, 3.40, 3.41, 3.42, 3.43, 3.44, 3.45, 3.46, 3.47, 3.48, 3.49, 3.50, 3.51, 3.52, 3.53, 3.54, 3.55, 3.56, 3.57, 3.58, 3.59, 3.60, 3.61, 3.62, 3.63, 3.64, 3.65, 3.66, 3.67, 3.68, 3.69, 3.70, 3.71, 3.72, 3.73, 3.74, 3.75, 3.76, 3.77, 3.78, 3.79, 3.80, 3.81, 3.82, 3.83, 3.84, 3.85, 3.86, 3.87, 3.88, 3.89, 3.90, 3.91, 3.92, 3.93, 3.94, 3.95, 3.96, 3.97, 3.98, 3.99, 4.00, 4.01, 4.02, 4.03, 4.04, 4.05, 4.06, 4.07, 4.08, 4.09, 4.10, 4.11, 4.12, 4.13, 4.14, 4.15, 4.16, 4.17, 4.18, 4.19, 4.20, 4.21, 4.22, 4.23, 4.24, 4.25, 4.26, 4.27, 4.28, 4.29, 4.30, 4.31, 4.32, 4.33, 4.34, 4.35, 4.36, 4.37, 4.38, 4.39, 4.40, 4.41, 4.42, 4.43, 4.44, 4.45, 4.46, 4.47, 4.48, 4.49, 4.50, 4.51, 4.52, 4.53, 4.54, 4.55, 4.56, 4.57, 4.58, 4.59, 4.60, 4.61, 4.62, 4.63, 4.64, 4.65, 4.66, 4.67, 4.68, 4.69, 4.70, 4.71, 4.72, 4.73, 4.74, 4.75, 4.76, 4.77, 4.78, 4.79, 4.80, 4.81, 4.82, 4.83, 4.84, 4.85, 4.86, 4.87, 4.88, 4.89, 4.90, 4.91, 4.92, 4.93, 4.94, 4.95, 4.96, 4.97, 4.98, 4.99, 5.00, 5.01, 5.02, 5.03, 5.04, 5.05, 5.06, 5.07, 5.08, 5.09, 5.10, 5.11, 5.12, 5.13, 5.14, 5.15, 5.16, 5.17, 5.18, 5.19, 5.20, 5.21, 5.22, 5.23, 5.24, 5.25, 5.26, 5.27, 5.28, 5.29, 5.30, 5.31, 5.32, 5.33, 5.34, 5.35, 5.36, 5.37, 5.38, 5.39, 5.40, 5.41, 5.42, 5.43, 5.44, 5.45, 5.46, 5.47, 5.48, 5.49, 5.50, 5.51, 5.52, 5.53, 5.54, 5.55, 5.56, 5.57, 5.58, 5.59, 5.60, 5.61, 5.62, 5.63, 5.64, 5.65, 5.66, 5.67, 5.68, 5.69, 5.70, 5.71, 5.72, 5.73, 5.74, 5.75, 5.76, 5.77, 5.78, 5.79, 5.80, 5.81, 5.82, 5.83, 5.84, 5.85, 5.86, 5.87, 5.88, 5.89, 5.90, 5.91, 5.92, 5.93, 5.94, 5.95, 5.96, 5.97, 5.98, 5.99, 6.00, 6.01, 6.02, 6.03, 6.04, 6.05, 6.06, 6.07, 6.08, 6.09, 6.10, 6.11, 6.12, 6.13, 6.14, 6.15, 6.16, 6.17, 6.18, 6.19, 6.20, 6.21, 6.22, 6.23, 6.24, 6.25, 6.26, 6.27, 6.28, 6.29, 6.30, 6.31, 6.32, 6.33, 6.34, 6.35, 6.36, 6.37, 6.38, 6.39, 6.40, 6.41, 6.42, 6.43, 6.44, 6.45, 6.46, 6.47, 6.48, 6.49, 6.50, 6.51, 6.52, 6.53, 6.54, 6.55, 6.56, 6.57, 6.58, 6.59, 6.60, 6.61, 6.62, 6.63, 6.64, 6.65, 6.66, 6.67, 6.68, 6.69, 6.70, 6.71, 6.72, 6.73, 6.74, 6.75, 6.76, 6.77, 6.78, 6.79, 6.80, 6.81, 6.82, 6.83, 6.84, 6.85, 6.86, 6.87, 6.88, 6.89, 6.90, 6.91, 6.92, 6.93, 6.94, 6.95, 6.96, 6.97, 6.98, 6.99, 7.00, 7.01, 7.02, 7.03, 7.04, 7.05, 7.06, 7.07, 7.08, 7.09, 7.10, 7.11, 7.12, 7.13, 7.14, 7.15, 7.16, 7.17, 7.18, 7.19, 7.20, 7.21, 7.22, 7.23, 7.24, 7.25, 7.26, 7.27, 7.28, 7.29, 7.30, 7.31, 7.32, 7.33, 7.34, 7.35, 7.36, 7.37, 7.38, 7.39, 7.40, 7.41, 7.42, 7.43, 7.44, 7.45, 7.46, 7.47, 7.48, 7.49, 7.50, 7.51, 7.52, 7.53, 7.54, 7.55, 7.56, 7.57, 7.58, 7.59, 7.60, 7.61, 7.62, 7.63, 7.64, 7.65, 7.66, 7.67, 7.68, 7.69, 7.70, 7.71, 7.72, 7.73, 7.74, 7.75, 7.76, 7.77, 7.78, 7.79, 7.80, 7.81, 7.82, 7.83, 7.84, 7.85, 7.86, 7.87, 7.88, 7.89, 7.90, 7.91, 7.92, 7.93, 7.94, 7.95, 7.96, 7.97, 7.98, 7.99, 8.00, 8.01, 8.02, 8.03, 8.04, 8.05, 8.06, 8.07, 8.08, 8.09, 8.10, 8.11, 8.12, 8.13, 8.14, 8.15, 8.16, 8.17, 8.18, 8.19, 8.20, 8.21, 8.22, 8.23, 8.24,

X^{25} is C_1 — H , C_2 — H , C_3 — H , C_4 — H , C_5 — H , or C_6 — H ; R^{80} is C_1 — C_6 or C_1 — C_6 branched alkyl.

[0004] The pyridazinone can serve as a Cox-2 selective inhibitor of the present invention. The pyridazinone compounds that are described in U.S. Patent 6,183,012 (2000) such pyridazinone compounds have the formula (A) shown as general formula XXXVI:



or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:
 X^{26} is a heteroatom selected from consisting of O, S, $-NR^{185}$, $-NOR^a$, and $-NNR^{186}$.

R¹²⁵ is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, cycloalkylalkyl, heterocyclic, and heterocycloalkyl.

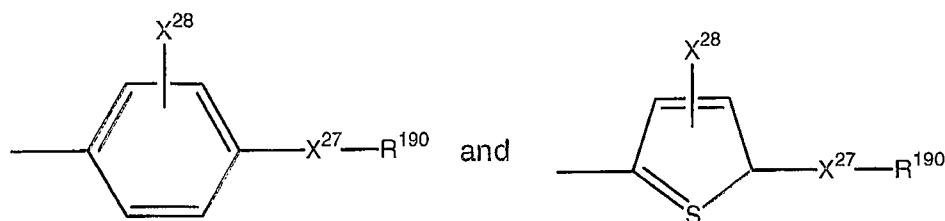
R^6, R^7 independently may be selected from the group consisting of all, 1-alkenyl, aryl, cycloalkyl, and cycloalkylalkyl;

[illegible]

- cycloalkenyl, cycloalkylidenealkyl, haloalkenyl, haloalkyl, haloalkenyl, haloalkyl, heterocyclic, heterocyclic alkyl, heterocyclic alkoxy, hydroxyalkyl, hydroxyiminoalkoxy, $G(O)R^{186}$, $-(CH_2)_n CH(OH)R^{186}$, $-(CH_2)_n$
- 5 $C(NR^d R^e)R^{186}$, $-(CH_2)_n CH(NR^d R^e)R^{186}$, $-R^{187}$, R^{187} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkylidene, cycloalkenyl, cycloalkyl, haloalkenyl, haloalkyl, haloalkenyl, heterocyclic alkyl;
- 10 R^{187} is selected from the group consisting of alkenylene, alkylene, halo-substituted alkylene, halo-substituted alkylene;
- R^{188} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkylidene, cycloalkenyl, cycloalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl;
- 15 R^0 is selected from the group consisting of hydrogen, alkyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkyl, heterocyclic alkyl;
- X^{23} is selected from the group consisting of hydrogen, alkyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkyl, heterocyclic alkyl;
- 20 m is an integer from 1 to 1000;
- n is an integer from 1 to 1000;
- p is an integer from 1 to 1000;
- R^{19} is independently selected from the group consisting of cyano, amino, alkoxy, alkoxyiminoalkoxy, alkoxyiminoalkyl, alkyl, alkylidene, cycloalkenyl, cycloalkyl, alkoxyalkylamino, alkylidenealkylamino, alkoxyalkylamino, aminoalkylcarbonyloxyalkoxy, aminoalkylcarbonyloxyalkyl, aryl, arylalkyl, arylalkynyl, carbonyl, carbonylalkoxy, cycloalkenyl, cycloalkyl, cycloalkylidene, cycloalkoxy, haloalkoxy, haloalkyl, halogen, heterocyclic, heterocyclic alkoxy, hydroxyiminoalkoxy, hydroxyiminoalkyl, heterocyclic alkyl, heterocyclic alkoxy, Y^8 , and Z^{14} ;
- 30

provided that one of R^{182} , R^{183} , or R^{184} must be Z^{14} , and further provided that only one of R^{182} , R^{183} , or R^{184} is Z^{14} ;

Z^{14} is selected from the group consisting of:



5

X^{27} is selected from the group consisting of S(O)_2 , $\text{S(O)(NR}^{191}\text{)}$, S(O) , Se(O)_2 , $\text{P(O)(OR}^{192}\text{)}$, and $\text{P(O)(NR}^{193}\text{R}^{194}\text{)}$;

X^{28} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl and halogen;

10

R^{190} is selected from the group consisting of alkenyl, alkoxy, alkyl, alkylamino, alkylcarbonylamino, alkynyl, amino, cycloalkenyl, cycloalkyl, dialkylamino, ---NHNH_2 , and $\text{---NCHN(R}^{191}\text{)R}^{192}$;

R^{191} , R^{192} , R^{193} , and R^{194} are independently selected from the group consisting of hydrogen, alkyl, and cycloalkyl, or R^{193} and R^{194} can be taken together, with the nitrogen to which they are attached, to form a 3-6 membered ring containing 1 or 2 heteroatoms selected from the group consisting of O, S, and NR^{188} ;

15

Y^8 is selected from the group consisting of ---OR^{195} , ---SR^{195} , $\text{---C(R}^{197}\text{)(R}^{198}\text{)R}^{195}$, ---C(O)R^{195} , ---C(O)OR^{195} , $\text{---N(R}^{197}\text{)C(O)R}^{195}$, $\text{---NC(R}^{197}\text{)R}^{195}$, and $\text{---N(R}^{197}\text{)R}^{195}$;

20

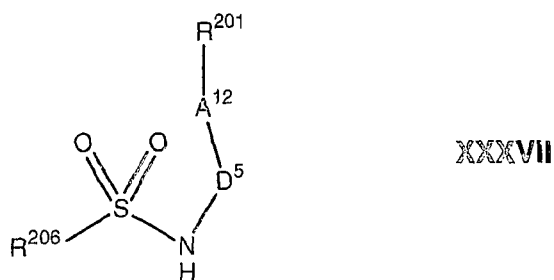
R^{195} is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkylthioalkyl, alkynyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, hydroxyalkyl, and $\text{NR}^{199}\text{R}^{200}$; and

25

R^{197} , R^{198} , R^{199} , and R^{200} are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkyl, cycloalkenyl, cycloalkyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl.

#15

[000150] Benzosulphonamide derivatives that are described in U.S. Patent No. 6,004,948 are useful as Cox-2 selective inhibitors of the present invention. Such benzosulphonamide derivatives have the formula shown below in formula XXXVII:



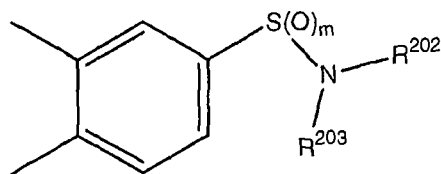
5

wherein:

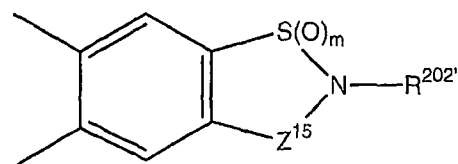
A¹² denotes oxygen, sulphur or NH;

R²⁰¹ denotes a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted by halogen, alkyl, CF₃ or alkoxy;

10 D⁵ denotes a group of formula XXXVIII or XXXIX:



or



15

R²⁰² and R²⁰³ independently of each other denote hydrogen, an optionally polyfluorinated alkyl radical, an aralkyl, aryl or heteroaryl radical or a radical (CH₂)_n-X²⁹; or

R²⁰² and R²⁰³ together with the N-atom denote a three- to seven-membered, saturated, partially or totally unsaturated heterocycle with one

or more heteroatoms N, O, or S, which may optionally be substituted by oxo, an alkyl, alkylaryl or aryl group or a group $(CH_2)_n - X^{29}$, R^{202} denotes hydrogen, an optionally polyfluorinated alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n - X^{29}$,

5 wherein:

X^{29} denotes halogen, NO_2 , $-OR^{204}$, $-COR^{204}$, $-CO_2 R^{204}$, $-OCO_2 R^{204}$, $-CN$, $-CONR^{204} OR^{205}$, $-CONR^{204} R^{205}$, $-SR^{204}$, $-S(O)R^{204}$, $-S(O)_2 R^{204}$, $-NR^{204} R^{205}$, $-NHC(O)R^{204}$, $-NHS(O)_2 R^{204}$;

10 Z^{15} denotes $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH=CH-$, $-CH=CH-CH_2-$, $-CH_2-CO-$, $-CO-CH_2-$, $-NHCO-$, $-CONH-$, $-NHCH_2-$, $-CH_2NH-$, $-N=CH-$, $-NHCH-$, $-CH_2-CH_2-NH-$, $-CH=CH-$, $>N-R^{203}$, $>C=O$, $>S(O)_m$;

R^{204} and R^{205} independently of each other denote hydrogen, alkyl, aralkyl or aryl;

15 n is an integer from 0 to 6;

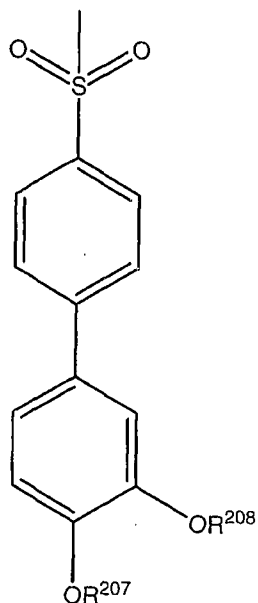
R^{206} is a straight-chained or branched $C_1 - C_4$ alkyl group which may optionally be mono- or polysubstituted by halogen or alkoxy, or R^{206} denotes CF_3 ; and

m denotes an integer from 0 to 2;

20 with the proviso that A^{12} does not represent O if R^{206} denotes CF_3 ; and the pharmaceutically acceptable salts thereof.

[000151] Materials that can serve as Cox-2 selective inhibitors of the present invention include methanesulfonyl-biphenyl derivatives that are described in U.S. Patent No. 6,583,321. Such methanesulfonyl-biphenyl derivatives have the formula shown below in formula **XXXX**:

25



XXXX

wherein:

R^{207} and R^{208} are respectively a hydrogen;

C_1 - C_4 -alkyl substituted or not substituted by halogens;

5 C_3 - C_7 -cycloalkyl;

C_1 - C_5 -alkyl containing 1-3 ether bonds and/or an aryl substitute;
substituted or not substituted phenyl;

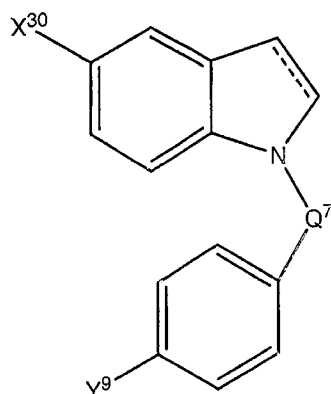
or substituted or not substituted five or six ring-cycled heteroaryl

10 containing more than one hetero atoms selected from a group consisting
of nitrogen, sulfur, and oxygen (wherein phenyl or heteroaryl can be one-
or multi-substituted by a substituent selected from a group consisting of
hydrogen, methyl, ethyl, and isopropyl).

[000152] Cox-2 selective inhibitors such as 1H-indole derivatives
described in U.S. Patent No. 6,599,929 are useful in the present invention.

15 Such 1H-indole derivatives have the formula shown below in formula

XXXXI:



XXXXXI

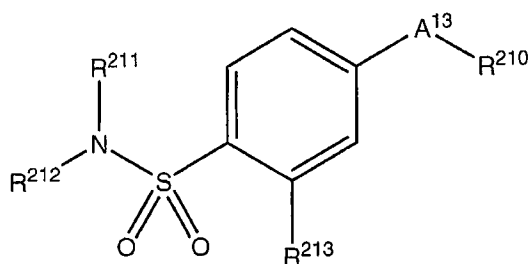
wherein:

X^{30} is $-NH\text{SO}_2R^{209}$ wherein R^{209} represents hydrogen or C_1-C_3 -alkyl;

Y^9 is hydrogen, halogen, C_1-C_3 -alkyl substituted or not substituted by halogen, NO_2 , NH_2 , OH , OMe , CO_2H , or CN ; and

Q^7 is $\text{C}=\text{O}$, $\text{C}=\text{S}$, or CH_2 .

[000153] Compounds that are useful as Cox-2 selective inhibitors of the present invention include prodrugs of Cox-2 inhibitors that are described in U.S. Patent Nos. 6,436,967 and 6,613,790. Such prodrugs of Cox-2 inhibitors have the formula shown below in formula XXXXII:



XXXXXII

wherein:

A^{13} is a ring substituent selected from partially unsaturated heterocyclic, heteroaryl, cycloalkenyl and aryl, wherein A^{13} is unsubstituted or substituted with one or more radicals selected from alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, nitro, carboxyl, alkoxy, aminocarbonyl, alkoxy carbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, haloalkylsulfonyloxy, alkoxyalkyloxyalkyl, carboxyalkoxyalkyl, cycloalkylalkyl, alkenyl, alkynyl, heterocycloxy, alkylthio, cycloalkyl, aryl,

heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, alkylthioalkyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, araalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, alkylamino, -arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminalkyl, N-aralkylaminoalkyl, N-alkyl-N-arylaminalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, and N-alkyl-N-arylaminosulfonyl;

R^{210} is selected from heterocyclyl, cycloalkyl, cycloalkenyl, and aryl, wherein R^{210} is unsubstituted or substituted with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^{211} is selected from hydrido and alkoxycarbonylalkyl;

R^{212} is selected from alkyl, carboxyalkyl, acyl, alkoxycarbonyl, heteroarylcarbonyl, alkoxycarbonylalkylcarbonyl, alkoxycarbonylcarbonyl, amino acid residue, and alkylcarbonylaminoalkylcarbonyl;

provided A^{13} is not tetrazolium, or pyridinium; and further provided A^{13} is not indanone when R^{212} is alkyl or carboxyalkyl; further provided A^{13} is not thienyl, when R^{210} is 4-fluorophenyl, when R^{211} is hydrido, and when R^{212} is methyl or acyl; and

R^{213} is hydrido;

or a pharmaceutically-acceptable salt thereof.

[000154] Specific non-limiting examples of substituted sulfonamide prodrugs of Cox-2 inhibitors disclosed in U.S. Patent No. 6,436,967 that are useful in the present invention include:

N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]propanamide;

N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]butanamide;

- N-[[4-[1,5-dimethyl)-3-phenyl-1H-pyrazol-4-yl]phenyl]sulfonyl]acetamide;
N-[[4-(2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)phenyl]sulfonyl]acetamide;
N-[[4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
5 N-[[4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]butanamide;
10 N-[[4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]butanamide;
N-[[4-[2-(3-chloro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[3-(3-fluorophenyl)-5-methylisoxazol-4-yl]phenyl]sulfonyl]acetamide;
15 2-methyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]benzamide;
2,2-dimethyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;
20 N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]butanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]pentanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]hexanamide;
3-methoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide ;
25 2-ethoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
N-[[4-[5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide;
N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]propanamide;
30 N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]butanamide;

- 12
- N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]acetamide;
- N-[[4-[3-(difluoromethyl)-6-fluoro-1,5-dihydro-7-methoxy-[2]benzothiopyrano [4,3-c]pyrazol-1-yl)phenyl]sulfonyl]acetamide;
- 5 N-[[4-[6-fluoro-1,5-dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyran o[4,3-c]pyrazol-1-yl]phenyl]sulfonyl]acetamide;
- N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]acetamide;
- N-[[4-(2-methyl-4-phenyloxazol-5-yl)phenyl]sulfonyl]acetamide;
- 10 methyl[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]oxoacetate;
- 2-methoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
- N-[[4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide;
- 15 N-[[4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]butanamide;
- N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]formamide;
- 1,1-dimethylethyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]carbamate;
- 20 N-[[.sup.4 -(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]glycine;
- 2-amino-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
- 2-(acetylamino)-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
- methyl 4-[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]-4-
- 25 oxobutanoate;
- methyl N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]carbamate;
- N-acetyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]glycine, ethyl ester;
- N-[[4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl]sulfonyl]acetamide;
- 30 methyl 3-[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]-3-oxopropanoate;

4-[5-(3-bromo-5-fluoro-4-methoxyphenyl)-2-(trifluoromethyl)oxazol-4-yl]-N-methylbenzenesulfonamide;

N-(1,1-dimethylethyl)-4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;

5 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-methylbenzenesulfonamide;

N-methyl-4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;

N-[[4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide;

N-[[4-[5-(acetoxymethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide;

10 N-[[4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]phenyl]sulfonyl]acetamide;

4-[2-(4-fluorophenyl)-1H-pyrrol-1-yl]-N-methylbenzenesulfonamide;

N-[[4-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)phenyl]sulfonyl]propanamide;

15 N-[[4-[2-(2-methylpyridin-3-yl)-4-trifluoromethylimidazol-1-yl]phenyl]sulfonyl]propanamide;

4-[2-(4-fluorophenyl)cyclopenten-1-yl]-N-methylbenzenesulfonamide; and

N-[[4-(3-phenyl-2,3-dihydro-2-oxofuran-4-yl)phenyl]sulfonyl]propanamide.

[000155] Those prodrugs disclosed in U.S. Patent No. 6,613,790 have the general formula shown above in formula **XXXXII** wherein:

20 A¹³ is a pyrazole group optionally substituted at a substitutable position with one or more radicals independently selected at each occurrence from the group consisting of alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, intro, carboxyl, alkoxy, aminocarbonyl, alkoxycarbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, haloalkylsulonyloxy, alkoxyalkyloxyalkyl, carboxyalkoxyalkyl, alkenyl, alkynyl, alkylthio, alkylthioalkyl, alkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, alkylaminocarbonylalkyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkylsutfinyl, alkylsulfonyl, aminosulfonyl, and alkylaminosulfonyl;

30 R²¹⁰ is a phenyl group optionally substituted at a substitutable position with one or more radicals independently selected at each occurrence from the group consisting of alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl,

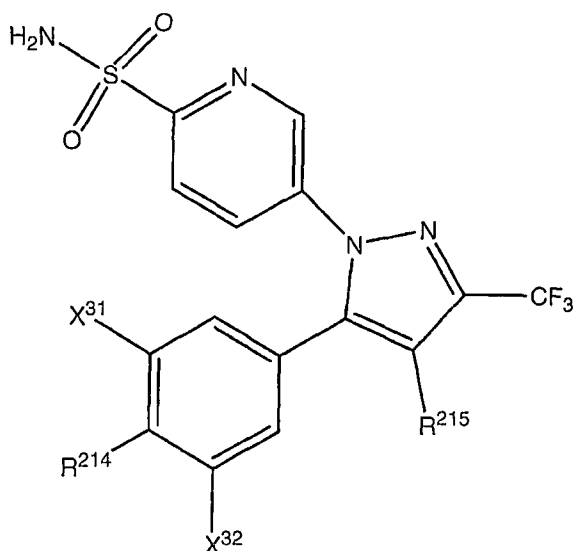
hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^{211} and R^{212} are independently selected from the group consisting of hydroxyalkyl and hydrido but at least one of R^{211} and R^{212} is other than hydrido; and

R^{213} is selected from the group consisting of hydrido and fluoro.

[000156] Examples of prodrug compounds disclosed in U.S. 6,613,790 that are useful as Cox-2 inhibitors of the present invention include, but are not limited to, N-(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, N,N-bis(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, or pharmaceutically-acceptable salts thereof.

[000157] Cox-2 selective inhibitors such as sulfamoylheleroaryl pyrazole compounds that are described in U.S. Patent No. 6,583,321 may serve as Cox-2 inhibitors of the present invention. Such sulfamoylheleroaryl pyrazole compounds have the formula shown below in formula **XXXXIII**:



XXXXIII

wherein:

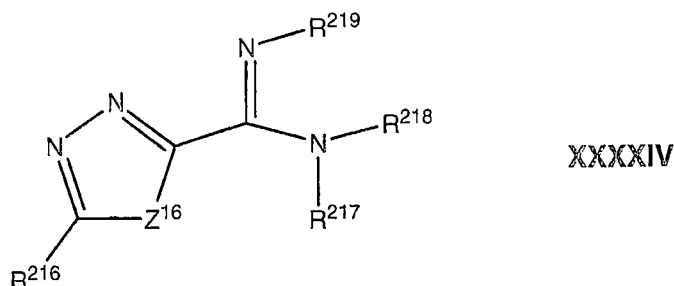
R^{214} is furyl, thiazolyl or oxazolyl;

R^{215} is hydrogen, fluoro or ethyl; and

X^{31} and X^{32} are independently hydrogen or chloro.

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[000158] Heteroaryl substituted amidinyl and imidazolyl compounds such as those described in U.S. Patent No. 6,555,563 are useful as Cox-2 selective inhibitors of the present invention. Such heteroaryl substituted amidinyl and imidazolyl compounds have the formula shown below in formula XXXXIV:



wherein:

Z¹⁶ is O or S,

10 R²¹⁶ is optionally substituted aryl,

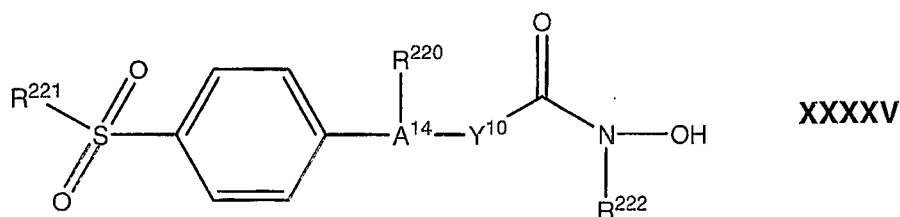
R²¹⁷ is aryl optionally substituted with aminosulfonyl, and

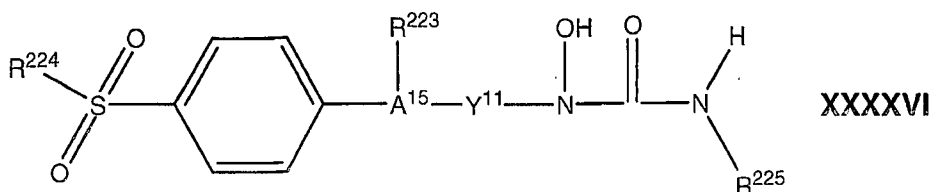
R²¹⁸ and R²¹⁹ cooperate to form an optionally substituted 5-membered ring.

[000159] Materials that can serve as Cox-2 selective inhibitors of the present invention include substituted hydroxamic acid derivatives that are described in U.S. Patent Nos. 6,432,999, 6,512,121, and 6,515,014.

These compounds also act as inhibitors of the lipxygenase-5 enzyme.

Such substituted hydroxamic acid derivatives have the general formulas shown below in formulas XXXXV and XXXXVI:





[000160] Pyrazole substituted hydroxamic acid derivatives described in U.S. Patent No. 6,432,999 have the formula shown above in formula XXXXV, wherein:

- 5 A^{14} is pyrazolyl optionally substituted with a substituent selected from acyl, halo, hydroxyl, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;
- Y^{10} is selected from lower alkenylene and lower alkynylene;
- 10 R^{220} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{220} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylmino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;
- 15 R^{221} is selected from lower alkyl and amino; and
- R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.
- 20

[000161] Pyrazole substituted hydroxamic acid derivatives described in U.S. Patent No. 6,432,999 may also have the formula shown above in formula XXXXVI, wherein:

- 25 A^{15} is pyrazolyl optionally substituted with a substituent selected from acyl, halo, hydroxyl, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;
- Y^{11} is selected from lower alkylene, lower alkenylene and lower alkynylene;

R^{223} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{223} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxy carbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylmino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{224} is selected from lower alkyl and amino; and

R^{225} is selected from hydrido, lower alkyl;

or a pharmaceutically-acceptable salt thereof.

[000162] Heterocyclo substituted hydroxamic acid derivatives described in U.S. Patent No. 6,512,121 have the formula shown above in formula **XXXXV**, wherein:

A^{14} is a ring substituent selected from oxazolyl, furyl, pyrrolyl, thiazolyl, imidazolyl, isochiazolyl, isoxazolyl, cyclopentenyl, phenyl, and pyridyl; wherein A^{14} is optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxy carbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{10} is lower alkylene, lower alkenylene, and lower alkynylene;

R^{220} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{220} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxy carbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{221} is selected from lower alkyl and amino; and

R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

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[000163] Heterocyclo substituted hydroxamic acid derivatives described in U.S. Patent No. 6,512,121 may also have the formula shown above in formula XXXXVI, wherein:

A¹⁵ is a ring substituent selected from oxazolyl, furyl, pyrrolyl, thiazolyl, imidazolyl, isothiazolyl, isoxazolyl, cyclopentenyl, phenyl, and pyridyl; wherein A is optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y¹¹ is selected from lower alkyl, lower alkenyl and lower alkynyl;

R²²³ is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R²²³ is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R²²⁴ is selected from lower alkyl and amino; and

R²²⁵ is selected from hydrido and alkyl; or a pharmaceutically-acceptable salt thereof.

[000164] Thiophene substituted hydroxamic acid derivatives described in U.S. Patent No. 6,515,014 have the formula shown above in formula XXXXV, wherein:

A¹⁴ is thienyl optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y¹⁰ is ethylene, isopropylene, propylene, butylene, lower alkenylene, and lower alkynylene;

R²²⁰ is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R²²⁰ is optionally substituted at a substitutable position

with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxy carbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfanyl, halo, lower alkoxy and lower alkylthio;

5 R^{221} is selected from lower alkyl and amino; and

R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

10 **[000165]** Thiophene substituted hydroxamic acid derivatives described in U.S. Patent No. 6,515,014 may also have the formula shown above in formula **XXXXV**, wherein:

A^{15} is thienyl optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxy carbonyl, lower carboxyalkyl, 15 lower cyanoalkyl, and lower hydroxyalkyl;

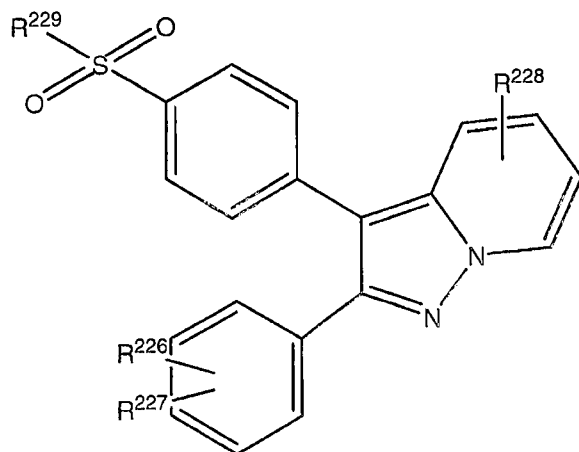
Y^{11} is selected from lower alkyl, lower alkenyl and lower alkynyl;

R^{223} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{223} is optionally substituted at a substitutable position 20 with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxy carbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfanyl, halo, lower alkoxy and lower alkylthio;

R^{224} is selected from lower alkyl and amino; and

25 R^{225} is selected from hydrido and alkyl; or a pharmaceutically-acceptable salt thereof.

[000166] Compounds that are useful as Cox-2 selective inhibitors of the present invention include pyrazolopyridine compounds that are described in U.S. Patent No. 6,498,166. Such pyrazolopyridine compounds have the 30 formula shown below in formula **XXXXVII**:



XXXXVII

wherein:

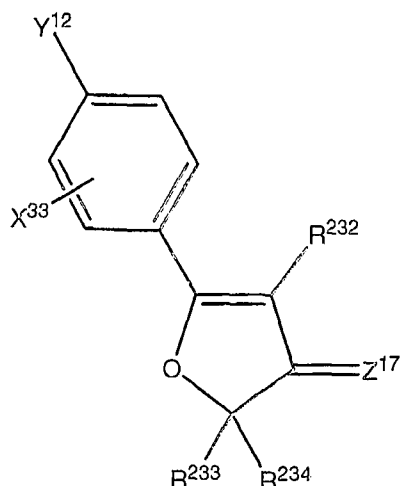
R^{226} and R^{227} are independently selected from the group consisting of H, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, and C_1-C_6 alkoxy substituted by one or more fluorine atoms;

R^{228} is halogen, CN, $CONR^{230}$, R^{231} , CO_2H , $CO_2C_1-C_6$ alkyl, or $NHSO_2R^{230}$;

R^{229} is C_1-C_6 alkyl or NH_2 ; and

R^{225} and R^{225} are independently selected from the group consisting of H, C_1-C_6 alkyl, phenyl, phenyl substituted by one or more atoms or groups selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, and C_1-C_6 alkoxy substituted by one or more fluorine atoms, or a pharmaceutically acceptable salt, solvate, ester, or salt or solvate of such ester thereof.

[000167] Materials that are useful as Cox-2 selective inhibitors of the present invention include 4,5-diaryl-3(2H)-furanone derivatives that are described in U.S. Patent No. 6,492,416. Such 4,5-diaryl-3(2H)-furanone derivatives have the formula shown below in formula XXXXVIII:



XXXXVIII

wherein:

X³³ represents halo, hydrido, or alkyl;

Y¹² represents alkylsulfonyl, aminosulfonyl, alkylsulfinyl, (N-acylamino)-
 5 sulfonyl, (N-alkylamino)sulfonyl, or alkylthio;

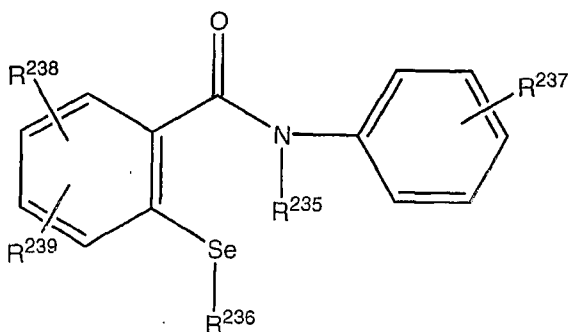
Z¹⁷ represents oxygen or sulfur atom;

R²³³ and R²³⁴ are selected independently from lower alkyl radicals;

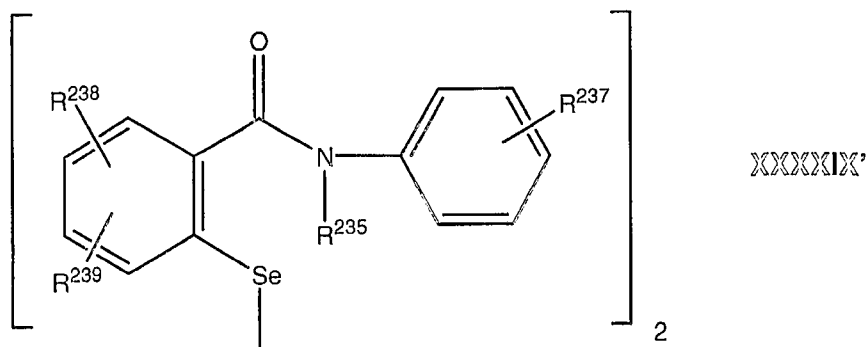
and R²³² represents a substituted or non-substituted aromatic group of 5 to
 10 atoms;

or a pharmaceutically-acceptable salt thereof.

[000168] Cox-2 selective inhibitors that can be used in the present
 invention include 2-phenyl-1,2-benzisoselenazol-3(2H)-one derivatives
 and 2-phenylcarbonyl-phenylselenenyl derivatives that are described in U.S.
 Patent No. 6,492,416. Such 2-phenyl-1,2-benzisoselenazol-3(2H)-one
 15 derivatives and 2-phenylcarbonyl-phenylselenenyl derivatives have the
 formulas shown below in formulas XXXXIX or XXXXIX':



XXXXIX



wherein:

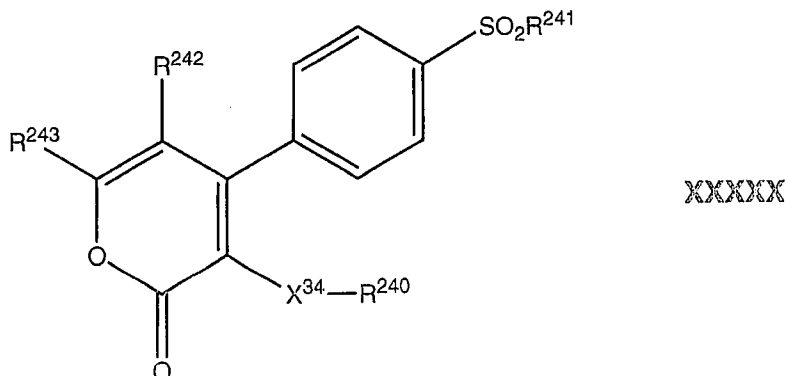
R^{235} is a hydrogen atom or an alkyl group having 1-3 carbon atoms;

R^{236} is a hydrogen atom, a hydroxyl group, an organothiol group that is bound to the selenium atom by its sulfur atom, or R^{235} and R^{236} are joined to each other by a single bond;

R^{237} is a hydrogen atom, a halogen atom, an alkyl group having 1-3 carbon atoms, an alkoxyl group having 1-3 carbon atoms, a trifluoromethyl group, or a nitro group;

R^{238} and R^{239} are identical to or different from each other, and each is a hydrogen atom, a halogen atom, an alkoxyl group having 1-4 carbon atoms, a trifluoromethyl group, or R^{238} and R^{239} are joined to each other to form a methylenedioxy group, a salt thereof, or a hydrate thereof.

[000169] Pyrones such as those disclosed in U.S. Patent No. 6,465,509 are also useful as Cox-2 inhibitors of the present invention. These pyrone compounds have the general formula shown below in formula **XXXXX**:



wherein:

X^{34} is selected from the group consisting of:

- (a) a bond,
- (b) $--(CH_2)_m--$, wherein m 1 or 2,
- (c) $--C(O)--$,
- 5 (d) $--O--$,
- (e) $--S--$, and
- (f) $--N(R^{244})--$;

R^{240} is selected from the group consisting of:

- 10 (a) $C_1 - C_{10}$ alkyl, optionally substituted with 1-3 substituents independently selected from the group consisting of: hydroxy, halo, $C_1 - C_{10}$ alkoxy, $C_1 - C_{10}$ alkylthio, and CN,
- (b) phenyl or naphthyl, and
- (c) heteroaryl, which is comprised of a monocyclic aromatic ring of 5 atoms having one hetero atom which is S, O or N, and optionally 1, 2, or 3
- 15 additional N atoms; or
- a monocyclic ring of 6 atoms having one hetero atom which is N, and optionally 1, 2, or 3 additional N atoms, wherein groups (b) and (c) above are each optionally substituted with 1-3 substituents independently selected from the group consisting of: halo, $C_1 - C_{10}$ alkoxy, $C_1 - C_{10}$
- 20 alkylthio, CN, $C_1 - C_{10}$ alkyl, optionally substituted to its maximum with halo, and N_3 ;

R^{241} is selected from the group consisting of

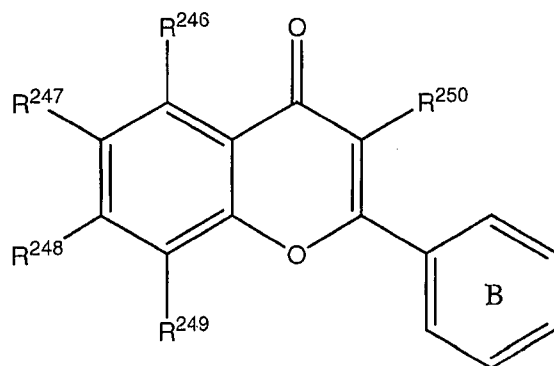
- (a) $C_1 - C_6$ alkyl, optionally substituted to its maximum with halo,
 - (b) NH_2 , and
 - 25 (c) $NHC(O)C_1 - C_{10}$ alkyl, optionally substituted to its maximum with halo;
- R^{242} and R^{243} are each independently selected from the group consisting of: hydrogen, halo, and $C_1 - C_6$ alkyl, optionally substituted to its maximum with halo; and

- 30 R^{244} is selected from the group consisting of: hydrogen and $C_1 - C_6$ alkyl, optionally substituted to its maximum with halo.

[000170] Examples of pyrone compounds that are useful as Cox-2 selective inhibitors of the present invention include, but are not limited to:

4-(4-Methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
 3-(4-Fluorophenyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
 3-(3-Fluorophenyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
 6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
 5 6-Difluoromethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
 6-Fluoromethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
 6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenylthio-pyran-2-one,
 6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenoxy-pyran-2-one,
 6-Methyl-4-(4-methylsulfonyl)phenyl-3-pyridin-3-yl-pyran-2-one,
 10 3-Isopropylthio-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
 4-(4-Methylsulfonyl)phenyl-3-phenylthio-6-trifluoromethyl-pyran-2-one,
 3-Isopropylthio-4-(4-methylsulfonyl)phenyl-6-trifluoromethyl-pyran-2-one,
 4-(4-Methylsulfonyl)phenyl-3-phenyl-6-(2,2,2-trifluoroethyl)-pyran-2-one,
 and
 15 3-(3-Hydroxy-3-methylbutyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one.

[000171] Organically synthesized or purified from plant sources, free-B-ring flavanoids such as those described in U.S. Published Application No. 2003/0165588, are useful as Cox-2 selective inhibitors of the present
 20 invention. Such free-B-ring flavanoids have the general structure shown in formula XXXXXI:



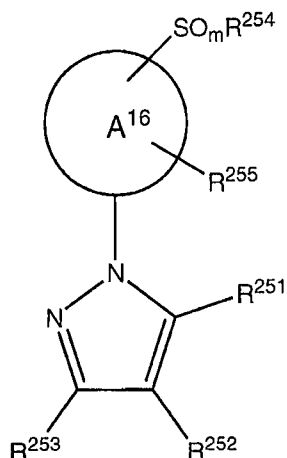
XXXXXI

wherein:

25 R^{246} , R^{247} , R^{248} , R^{249} , and R^{250} are independently selected from the group consisting of: --H, --OH, --SH, --OR, --SR, --NH₂, --NHR²⁴⁵, --N(R²⁴⁵)₂,

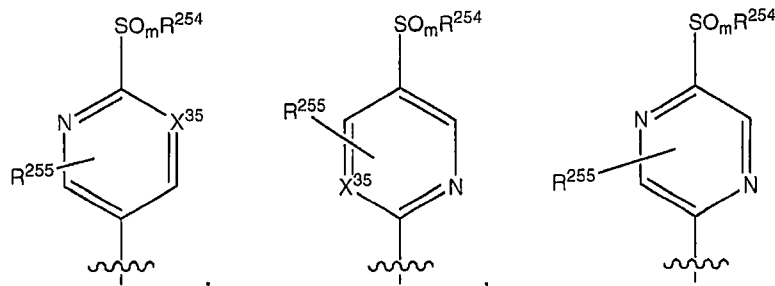
--N(R²⁴⁵)₃⁺X³⁵⁻, a carbon, oxygen, nitrogen or sulfur, glycoside of a single or a combination of multiple sugars including, aldopentoses, methyl-aldopentose, aldohexoses, ketohexose and their chemical derivatives thereof; wherein R²⁴⁵ is an alkyl group having between 1-10 carbon atoms; and X³⁵ is selected from the group of pharmaceutically acceptable counter anions including, hydroxyl, chloride, iodide, sulfate, phosphate, acetate, fluoride and carbonate.

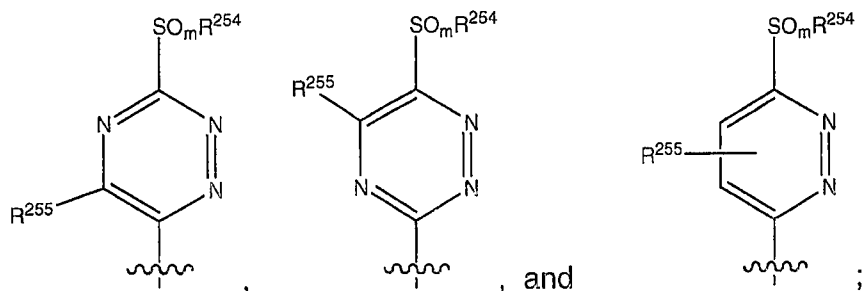
[000172] Heterocyclo-alkylsulfonyl pyrazoles such as those described in European Patent Application No. EP 1312367 are useful as Cox-2 selective inhibitors of the present invention. Such heterocyclo-alkylsulfonyl pyrazoles have the general formula shown below in formula **XXXXXXII**:

**XXXXXXII**

or a pharmaceutically acceptable salt thereof, wherein:

the ring of the formula (R²⁵⁵)-A-(SO_mR²⁵⁴) is selected from the group consisting of:





m is 0, 1 or 2;

X^{35} is $>CR^{255}$ or $>N$;

- R^{251} is a radical selected from the group consisting of H, NO_2 , CN, $(C_1 - C_8)alkyl$, $(C_1 - C_6)alkyl-SO_2-$, $(C_6 - C_{10})aryl-SO_2-$, $H-(C=O)-$, $(C_1 - C_6)alkyl-(C=O)-$, $(C_1 - C_6)alkyl-(C=O)-$, $(C_1 - C_9)heteroaryl-(C=O)-$, $(C_1 - C_9)heterocyclyl-(C=O)-$, $H_2N-(C=O)-$, $(C_1 - C_6)alkyl-NH-(C=O)-$, $[(C_1 - C_6)alkyl]_2-N-(C=O)-$, $[(C_6 - C_{10})aryl]_2-NH-(C=O)-$, $[(C_1 - C_6)alkyl]-[(C_6 - C_{10})aryl-N]-(C=O)-$, $HO-NH-(C=O)-$, and $(C_1 - C_6)alkyl-O-NH-(C=O)-$;
- R^{252} is a radical selected from the group consisting of H, $-NO_2$, $-CN$, $(C_2 - C_6)alkenyl$, $(C_2 - C_6)alkynyl$, $(C_3 - C_7)cycloalkyl$, $(C_6 - C_{10})aryl$, $(C_1 - C_9)heteroaryl$, $(C_1 - C_9)heterocyclyl$, $(C_1 - C_6)alkyl-O-$, $(C_3 - C_7)cycloalkyl-O-$, $(C_6 - C_{10})aryl-O-$, $(C_1 - C_9)heteroaryl-O-$, $(C_6 - C_9)heterocyclyl-O-$, $H-(C=O)-$, $(C_1 - C_6)alkyl-(C=O)-$, $(C_3 - C_7)cycloalkyl-(C=O)-$, $(C_6 - C_{10})aryl-(C=O)-$, $(C_1 - C_9)heteroaryl-(C=O)-$, $(C_1 - C_9)heterocyclyl-(C=O)-$, $(C_1 - C_6)alkyl-O-(C=O)-$, $(C_3 - C_7)cycloalkyl-O-(C=O)-$, $(C_6 - C_{10})aryl-O-(C=O)-$, $(C_1 - C_9)heteroaryl-O-(C=O)-$, $(C_1 - C_9)heterocyclyl-O-(C=O)-$, $(C_1 - C_6)alkyl-(C=O)-O-$, $(C_3 - C_7)cycloalkyl-(C=O)-O-$, $(C_6 - C_{10})aryl-(C=O)-O-$, $(C_1 - C_9)heteroaryl-(C=O)-O-$, $(C_1 - C_9)heterocyclyl-(C=O)-O-$, $(C_1 - C_6)alkyl-(C=O)-NH-$, $(C_3 - C_7)cycloalkyl-(C=O)-NH-$, $(C_6 - C_{10})aryl-(C=O)-NH-$, $(C_1 - C_9)heteroaryl-(C=O)-NH-$, $(C_1 - C_9)heterocyclyl-(C=O)-NH-$, $(C_1 - C_6)alkyl-O-(C=O)-NH-$, $(C_1 - C_6)alkyl-NH$, $[(C_1 - C_6)alkyl]_2-N-$, $(C_3 - C_7)cycloalkyl-NH-$, $[(C_3 - C_7)cycloalkyl]_2-N-$, $[(C_6 - C_{10})aryl]-NH-$, $[(C_6 - C_{10})aryl]_2-N-$, $[(C_1 - C_6)alkyl]-[(C_6 - C_{10})aryl-N]-$, $[(C_1 - C_9)heteroaryl]-NH-$, $[(C_1 - C_9)heteroaryl]_2-N-$, $[(C_1 - C_9)heterocyclyl]-NH-$, $[(C_1 - C_9)heterocyclyl]_2-N-$, $H_2N-(C=O)-$, $HO-NH-(C=O)-$, $(C_1 - C_6)alkyl-O-NH-(C=O)-$, $[(C_1 - C_6)alkyl]-NH-(C=O)-$, $[(C_1 - C_6)alkyl]_2-N-(C=O)-$, $[(C_3 - C_7)cycloalkyl]-NH-(C=O)-$, $[(C_3 - C_7)cycloalkyl]_2-N-(C=O)-$, $[(C_6 - C_{10})aryl]-NH-$

(C=O)-, [(C₆-C₁₀aryl)₂-N-(C=O)-, [(C₁-C₆)alkyl]-[[(C₆-C₁₀)aryl]-N]-(C=O)-, [(C₁-C₉)heteroaryl]-NH-(C=O)-, [(C₁-C₉)heteroaryl]₂-N-(O=O)-, [(C₁-C₉)heterocyclyl]-NH-(C=O)-, (C₁-C₆)alkyl-S- and (C₁-C₆)alkyl optionally substituted by one -OH substituent or by one to four fluoro substituents;

5 R²⁵³ is a saturated (3- to 4-membered)-heterocyclyl ring radical; or a saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical;

wherein said saturated (3- to 4-membered)-heterocyclyl ring radical or said saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical; may optionally contain one to four ring heteroatoms independently selected from the groups consisting of -N=, -NH-, -O-, and -S-;

wherein said saturated (3- to 4-membered)-heterocyclyl ring radical; or said saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical; may optionally be substituted on any ring carbon atom by one to three substituents per ring independently selected from the group consisting of halo, -OH, -CN, -NO₂, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)cycloalkyl, (C₆-C₁₀)aryl, (C₂-C₉)heterocyclyl, (C₁-C₆)alkyl-O-, H-(C=O)-, (C₁-C₆)alkyl-(C=O)-, HO-(C=O)-, (C₁-C₆)alkyl-O-(C=O)-, -NH₂, (C₁-C₆)alkyl-NH-, [(C₁-C₆)alkyl]₂-N-, (C₃-C₇)cycloalkyl-NH-, (C₆-C₁₀)aryl-NH-, [(C₁-C₆)alkyl]-[[(C₆-C₁₀)aryl]-N]-, (C₁-C₉)heteroaryl-NH-, H₂N-(C=O)-[(C₁-C₆)alkyl]-NH-(C=O)-, [(C₁-C₆)alkyl]₂-N-(C=O)-, [(C₆-C₁₀)aryl]-NH-(C=O)-, [(C₁-C₆)alkyl]-[[(C₆-C₁₀)aryl]-N]-(C=O)-, (C₁-C₆)alkyl-O-NH-(C=O)-, (C₁-C₆)alkyl-(C=O)-HN-, (C₁-C₆)alkyl-(C=O)-[(C₁-C₆)alkyl-N]-, -SH, (C₁-C₆)alkyl-S-, (C₁-C₆)alkyl-(S=O)-, (C₁-C₆)alkyl-SO₂- and (C₁-C₆)alkyl optionally substituted with one to four fluoro moieties;

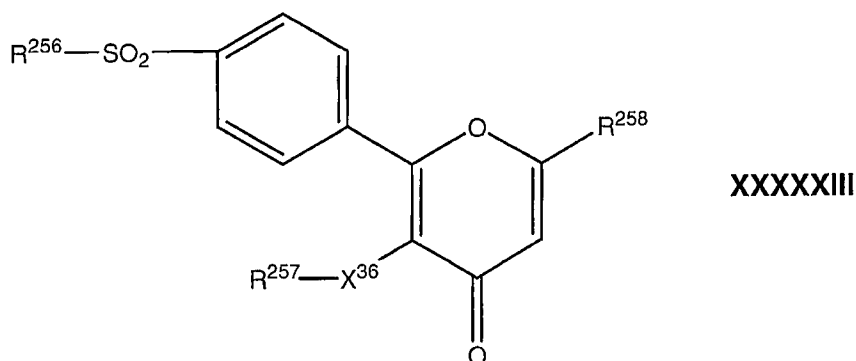
wherein said saturated (3- to 4-membered)-heterocyclyl ring radical; or said saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical; may also optionally be substituted on any ring nitrogen atom by one to three substituents per ring independently selected from the group consisting of (C₃-C₇)cycloalkyl, (C₆-C₁₀)aryl, (C₂-

C₉)heterocyclyl, H-(C=O)-, (C₁-C₆)alkyl-(C=O)-, (C₁-C₆)alkyl-O-(C=O)-, H₂N-(C=O)-, [(C₁-C₆)alkyl]-NH-(C=O)-, [(C₁-C₆)alkyl]₂-N-(C=O)-, [(C₆-C₁₀)aryl]-NH-(C=O)-, [(C₁-C₆)alkyl]-[(C₆-C₁₀)aryl]-N-(C=O)-, (C₁-C₆)alkyl-O-NH-(C=O)-, and (C₁-C₆)alkyl optionally substituted with one to four fluoro moieties;

R²⁵⁴ is an (C₁-C₆)alkyl radical optionally substituted by one to four fluoro substituents; and

R²⁵⁵ is a radical selected from the group consisting of H, halo, -OH, (C₁-C₆)alkyl-O-, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)cycloalkyl, -CN, H-(C=O)-, (C₁-C₆)alkyl-(C=O)-, (C₁-C₆)alkyl-(C=O)-O-, HO-(C=O)-, (C₁-C₆)alkyl-O-(C=O)-, (C₁-C₆)alkyl-NH-, [(C₁-C₆)alkyl]₂-N-, (C₃-C₇)cycloalkyl-NH-, (C₆-C₁₀)aryl-NH-, [(C₁-C₆)alkyl]-[(C₆-C₁₀)aryl]-N-, (C₁-C₉)heteroaryl-NH-, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)-, [(C₁-C₆)alkyl]₂-N-(C=O)-, (C₆-C₁₀)aryl-(C=O)-, [(C₁-C₆)alkyl]-[(C₆-C₁₀)aryl]-N-(C=O)-, (C₁-C₆)alkyl-O-NH-(C=O)-, (C₁-C₆)alkyl-S-, and (C₁-C₆)alkyl optionally substituted by one to four fluoro substituents.

[000173] 2-phenylpyran-4-one derivatives such as those described in U.S. Patent No. 6,518,303 are also useful as Cox-2 selective inhibitors of the present invention. Such 2-phenylpyran-4-one derivatives have the general formula shown below in formula XXXXXIII:



wherein:

R²⁵⁶ represents an alkyl or -NR²⁵⁹R²⁶⁰ group, wherein R²⁵⁹ and R²⁶⁰ each independently represents a hydrogen atom or an alkyl group;

R²⁵⁷ represents an alkyl, C₃-C₇ cycloalkyl, naphthyl, tetrahydronaphthyl or

indanyl group, or a phenyl group which may be unsubstituted or substituted by one or more halogen atoms or alkyl, trifluoromethyl, hydroxy, alkoxy, methylthio, amino, mono- or dialkylamino, hydroxyalkyl or hydroxycarbonyl groups;

- 5 R^{258} represents a methyl, hydroxymethyl, alkoxymethyl, $C_3 - C_7$ cycloalkoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group or a $CH_2 - R^{261}$ group wherein R^{261} represents an alkyl group; and
- 10 X^{36} represents a single bond, an oxygen atom, a sulfur atom or a methylene group;
- or a pharmaceutically acceptable salt thereof.

[000174] Examples of 2-phenylpyran-4-one derivatives useful in the present invention include, but are not limited to:

- 15 3-(4-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
 3-(2-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
 3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
 3-(4-bromophenyl)-2-(4-methylsulfonylphenyl)-6-methylpyran-4-one,
 3-(2,4-difluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
 3-(3,4-dichlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
 20 3-(3-chloro-4-methylphenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one ,
 2-(4-methanesulfonylphenyl)-6-methyl-3-phenoxy pyran-4-one,
 3-(4-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
 3-(2-fluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
 25 3-(4-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
 3-(2-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
 3-(4-bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
 2-(4-methanesulfonylphenyl)-6-methyl-3-(4-methylphenoxy)pyran-4-one,
 3-(2,4-difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
 30 one,
 3-(2,5-difluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
 3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran-4-

one,

3-(4-chlorophenyl)-6-difluoromethyl-2-(4-methanesulfonylphenyl)pyran-4-

one,

and pharmaceutically acceptable salts thereof.

5 [000175] Cox-2 selective inhibitors that are useful in the subject method and compositions can also include the compounds that are described in U.S. Patent No. 6,472,416 (sulfonylphenylpyrazoles); U.S. Patent No. 6,451,794 (2,3-diaryl-pyrazolo[1,5-b]pyridazines); U.S. Patent Nos. 6,169,188, 6,020,343, and 5,981,576 ((methylsulfonyl)phenyl furanones);
10 U.S. Patent No. 6,222,048 (diaryl-2-(5H)-furanones); U.S. Patent No. 6,057,319 (3,4-diaryl-2-hydroxy-2,5-dihydrofurans); U.S. Patent No. 6,046,236 (carbocyclic sulfonamides); U.S. Patent Nos. 6,002,014 and 5,945,539 (oxazole derivatives); U.S. Patent Nos. 6,359,182 and 6,538,116 (C-nitroso compounds); U.S. Published Application No.
15 2003/0065011 (substituted pyridines); U.S. Published Application No. 2003/0207897 (substituted indole derivatives); and mixtures thereof.

[000176] Examples of specific compounds that are useful as Cox-2 selective inhibitors include, without limitation:

- 20 a1) 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;
a2) 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;
a3) 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;
a4) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;
25 a5) 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide
a6) 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
a7) 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;
30 a8) 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

- a9) 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- a10) 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- 5 b1) 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- b2) 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide
- b3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 10 b4) 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- b5) 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- b6) 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 15 b7) 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- b8) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- b9) 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 20 b10) 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- c1) 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
- c2) 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 25 c3) 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- c4) 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- c5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 30 c6) 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

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- c7) 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- c8) 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 5 c9) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- c10) 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- d1) 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;
- d2) 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 10 d3) 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- d4) 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- d5) 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 15 d6) 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- d7) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
- 20 d8) 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
- d9) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;
- d10) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
- 25 e1) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;
- e2) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;
- e3) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;
- 30 e4) 2-[(3,5-dichlorophenoxy)methyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;

- e5) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
- e6) 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;
- 5 e7) 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;
- e8) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;
- 10 e9) 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;
- e10) 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;
- f1) 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;
- 15 f2) 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;
- f3) 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- f4) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 20 f5) 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- f6) 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 25 f7) 2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- f8) 2-methyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- f9) 2-methyl-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 30 f10) 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

- g1) 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- g2) 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 5 g3) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;
- g4) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;
- 10 g5) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- g6) 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- g7) 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;
- 15 g8) 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- g9) 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- g10) 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 20 h1) 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- h2) 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 25 h3) 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- h4) 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
- h5) 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 30 h6) 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

- h7) 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- h8) 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
- 5 h9) 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;
- i1) N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;
- i2) ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;
- 10 i3) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;
- i4) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;
- 15 i5) 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
- i6) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;
- i7) 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;
- 20 i8) 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- i9) 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- 25 i10) 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;
- j1) 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- j2) 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;
- 30 j3) 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;
- j4) 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;

- j5) 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;
j6) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
j7) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
j8) 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;
5 j9) 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
j10) 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
k1) 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
k2) 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
10 k3) 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
k4) 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
15 k5) 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
k6) 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;
k7) 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
20 k8) 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;
k9) 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
k10) 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;
25 l1) 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
l2) 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
l3) 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;
30 l4) 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

- l5) 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
l6) 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;
l7) ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-
2-benzyl-acetate;
5 l8) 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic
acid;
l9) 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
l10) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;
m1) 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole;
10 and
m2) 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-
oxazolyl]benzenesulfonamide.
m3) 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
m4) 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic
15 acid;
m5) 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic
acid;
m6) 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-
carboxylic acid;
20 m7) 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-
carboxylic acid;
m8) 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid ;
m9) 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-
carboxylic acid;
25 m10) 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
n1) 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
n2) 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic
acid;
n3) 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
30 n4) 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
n5) 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

- n6) 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n7) 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 5 n8) 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n9) 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n10) 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 10 o1) 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o2) 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o3) 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o4) 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid;
- 15 o5) 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o6) 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o7) 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 20 o8) 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o9) 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 25 o10) 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p1) 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p2) 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 30 p3) 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

- p4) 6-[(phenylmethyl)amino]sulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p5) 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 5 p6) 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p7) 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 10 p8) 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p9) 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p10) 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 15 q1) 8-chloro-6-[(phenylmethyl)amino]sulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q2) 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q3) 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q4) 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 20 q5) 6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q6) 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 25 q7) 6-[N-(2-furylmethyl)amino]sulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q8) 6-[N-(2-phenylethyl)amino]sulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q9) 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 30 q10) 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid;

- r1) 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methyl-sulphonyl-2(5H)-fluranone;
- r2) 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;
- r3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 5 r4) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- r5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 10 r6) 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
- r7) 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
- r8) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 15 r9) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- r10) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- s1) [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
- 20 s2) 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; or
- s3) 4-[5-(3-fluoro-4-methoxyphenyl-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide;
- or a pharmaceutically acceptable salt or prodrug thereof.
- [000177]** Preferred Cox-2 selective inhibitor compounds are those
- 25 compounds selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, etoricoxib, meloxicam, rofecoxib, lumiracoxib, RS 57067, T-614, BMS-347070 (Bristol Meyers Squibb, described in U.S. Patent No. 6,180,651), JTE-522 (Japan Tobacco), S-2474 (Shionogi), SVT-2016, CT-3 (Atlantic Pharmaceutical), ABT-963 (Abbott), SC-58125
- 30 (GD Searle), nimesulide, flosulide, NS-398 (Taisho Pharmaceutical), L-745337 (Merck), RWJ-63556, L-784512 (Merck), darbufelone (Pfizer), CS-502 (Sankyo), LAS-34475 (Almirall Prodesfarma), LAS-34555 (Almirall

Prodesfarma), S-33516 (Servier), SD-8381 (Pharmacia, described in U.S. Patent No. 6,034,025), MK-966 (Merck), L-783,003 (Merck), T-614 (Toyama), D-1376 (Chiroscience), L-748,731 (Merck), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253,035 (Glaxo Wellcome),
5 prodrugs of any of them, and mixtures thereof.

[000178] More preferred is that the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, lumiracoxib, etoricoxib, rofecoxib, prodrugs of any of them, and mixtures thereof.

10 **[000179]** Even more preferred still is that the Cox-2 selective inhibitor is celecoxib.

[000180] Cox-2 inhibitors that are useful in the methods and compositions of present invention can be supplied by any source as long as the Cox-2 inhibitor is pharmaceutically acceptable. Cox-2 inhibitors can
15 also be isolated and purified from natural sources. Cox-2 inhibitors should be of a quality and purity that is conventional in the trade for use in pharmaceutical products.

[000181] Cox-2 inhibitors that are useful in the compositions and methods of present invention can also be synthesized, for example,
20 according to the description in Example 1. Several Cox-2 inhibitors that are suitable for use with the compositions and methods of the present invention may be synthesized by the methods described in, for example, in U.S. Patent No. 5,466,823 to Talley, *et al.*

[000182] By way of example, various classes of Cox-2 inhibitors useful
25 in the present invention can be prepared as follows. Pyrazoles can be prepared by methods described in WO 95/15316. Pyrazoles can further be prepared by methods described in WO 95/15315. Pyrazoles can also be prepared by methods described in WO 96/03385.

[000183] Thiophene analogs useful in the present invention can be
30 prepared by methods described in WO 95/00501. Preparation of thiophene analogs is also described in WO 94/15932.

[000184] Oxazoles useful in the present invention can be prepared by the methods described in WO 95/00501. Preparation of oxazoles is also described in WO 94/27980.

5 [000185] Isoxazoles useful in the present invention can be prepared by the methods described in WO 96/25405.

[000186] Imidazoles useful in the present invention can be prepared by the methods described in WO 96/03388. Preparation of imidazoles is also described in WO 96/03387.

10 [000187] Cyclopentene Cox-2 inhibitors useful in the present invention can be prepared by the methods described in U.S. Patent No. 5,344,991. Preparation of cyclopentene Cox-2 inhibitors is also described in WO 95/00501.

[000188] Terphenyl compounds useful in the present invention can be prepared by the methods described in WO 96/16934.

15 [000189] Thiazole compounds useful in the present invention can be prepared by the methods described in WO 96/03,392.

[000190] Pyridine compounds useful in the present invention can be prepared by the methods described in WO 96/03392. Preparation of pyridine compounds is also described in WO 96/24,585.

20 [000191] Benzopyranopyrazolyl compounds useful in the present invention can be prepared by the methods described in WO 96/09304.

[000192] Chromene compounds useful in the present invention can be prepared by the methods described in WO 98/47890. Preparation of chromene compounds is also described in WO 00/23433. Chromene compounds can further be prepared by the methods described in U.S. Patent No. 6,077,850. Preparation of chromene compounds is further described in U.S. Patent No. 6,034,256.

25 [000193] Arylpyridazinones useful in the present invention can be prepared by the methods described in WO 00/24719. Preparation of arylpyridazinones is also described in WO 99/10332. Arylpyridazinones can further be prepared by the methods described in WO 99/10331.

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[000194] 5-Alkyl-2-arylaminophenylacetic acids and derivatives useful in the present invention can be prepared by the methods described in WO 99/11605.

5 [000195] Diarylmethylidenefuran derivative Cox-2 selective inhibitors useful in the present invention can be prepared by the methods described in U.S. Patent No. 6,180,651.

[000196] The celecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,466,823.

10 [000197] The valdecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,633,272.

15 [000198] The parecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,932,598.

[000199] The rofecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,474,995.

20 [000200] The deracoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,521,207.

[000201] The etoricoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 98/03484.

25 [000202] The meloxicam used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,233,299.

30 [000203] The compound 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,994,381.

[000204] The compound 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 00/24719.

5 [000205] The compound 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one used in the compositions and methods of the present invention can be prepared in the manner set forth in EP 863134.

10 [000206] The compound 2-[(2-chloro-6-fluorophenyl)amino]-5-methylbenzeneacetic acid used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 99/11605.

15 [000207] The compound N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,885,367.

[000208] The compound (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 6,180,651.

20 [000209] An optional second component of the present invention is a weight-loss agent that is administered to a subject in combination with a Cox-2 inhibitor.

25 [000210] The present invention is directed to a novel method of treating or preventing obesity and obesity-related complications in a subject comprising administering to the subject a Cox-2 inhibitor and one or more weight-loss agents.

30 [000211] As used herein, the term "weight-loss agent" refers to any chemical recognized as having an effect on a subject's weight over any duration of time other than a chemical that is an inhibitor of the Cox-2 enzyme. This effect can occur via appetite suppression, metabolic acceleration, adipogenesis inhibition, or any other mechanism. While not

to be construed as limiting, preferred examples of weight-loss agents are recited in Table 3 below.

- 5 [000212] Although, any combination of a Cox-2 inhibitor and weight-loss agent is encompassed by the present invention, preferred examples of weight-loss agents include those agents specifically recited in Table 3. Thus, it is further preferred that any weight-loss agent recited in Table 3 be combined in methods, compositions, pharmaceutical compositions, and kits with any Cox-2 inhibitor, and in preferred embodiments, any Cox-2 inhibitor that is described herein.

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Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A1	phenentermine	Adipex, Fastin, Ionamin, Oby-trim	anorectic		15-30 mg daily	
A2	diethylpropion	Tenuate, Tenuate dospan, Tepanil	anorectic Catecholamine modulator	1-phenyl-2- diethyl-amino- 1-propanone hydrochloride	25 mg three times daily	
A3	mazindol	Sanorex, Mazanor	anorectic Catecholamine modulator		1-3 mg daily	
A4	phendimetrazine	Adipost, Bontril, Plegine, Prelu-2, X- Trozone	anorectic		35 mg twice or three times daily	
A5	benzphetamine	Didrex	anorectic		25 to 50 mg one to three times daily	
A6	sibutramine	Meridia	norepinephrine,	cyclobutaneme	5 to 30 mg	

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
			dopamine and serotonin reuptake inhibitor and Catecholamine modulator	thanamine 1-(4-chlorophenyl)-N, N-dimethyl- α -(2-methylpropyl)-, hydrochloride	daily	
A7	orlistat	Xenical	Lipase inhibitor	(S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]-dodecyl ester	120 mg three times daily	
A8	fenfluramine	Pondimin	anorectic	N-ethyl- α -methyl-3-(trifluoromethyl)benzeneethanamine hydrochloride	20 mg three times daily	

Table 3: Weight-Loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A9	dexfenfluramine	Redux	dual serotonin reuptake inhibitor and serotonin releasing agent	(S)-N-ethyl-alpha-methyl-3-(trifluoromethyl)benzeneethanamine hydrochloride	15 to 30 mg daily	
A10	bupropion	Wellbutrin	aminoketone class antidepressant and is a serotonin reuptake inhibitor	(±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride	150mg given twice daily	
A11	diazoxide	Proglycem	Activator of ATP-dependent K ⁺ channels	7-chloro-3-methyl-2H-1,2,4-benzothiazine-1,1-dioxide		
A12	Dehydro-epiandrosterone		metabolic accelerator			U.S. Patent No. 5,795,880 to Svec, et al.
A13	metformin	Glucophage	anti-hyperglycemic	N,N-dimethylimidodimethyldi		

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Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A14	sertraline	Zoloft	serotonin reuptake inhibitor	carbonimidic diamide hydrochloride (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride		
A15	topiramate	Topamax	GABA enhancer and sodium channel blocker	2,3:4,5-bis-O-(1-methylethylidene)- β -D-fructopyranose sulfamate		
A16	(+) norfenfluramine		Serotonin and dopamine releaser			
A17	leptin derivatives and formulations					U.S. Patent Nos. 5,552,524; 5,552,523; 5,552,522; 5,521,283

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A18			Histamine-3 antagonist			
A19	rimonabant		cannabinoid (CB1) receptor antagonist			
A20	aminorex		anorectic			
A21	adiponectin					
A22	phenylpropanolamine	Control, Dexatrim, Phenoxine	Alpha-adrenergic receptor agonists		25-100 mg daily	
A23	amantadine	Symmetrel	anorectic			
A24	nizatidine		anorectic			
A25	cimetidine					
A26	amphetamine		B-phenethylamine			
A27	dinitrophenol					
A28	diethylpropion hydrochloride					
A29	mazindol benzphetamine					

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A30	phendimetrazine					
A31	phentermine		Catecholamine modulator			
A32	dexfenfluramine					
A33	amylin					
A34			melanocortin-4 receptor agonists			
A35			neuropeptide Y antagonists			WO 96/16542
A36			Beta(3)-adrenergic agonists			U.S. Pat. No. 5,541,677 and WO 95/29159
A37			glucagon-like peptide-1 agonists			
A38			PPAR-gamma antagonists and PPAR-gamma partial agonists			
A39			orexins			
A40			Dehydroepiandrosterone derivatives			

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A41	mazindol					
A42	ephedrine	Ephedra				
A43	fenfluramine			N-ethyl-.alpha.-methyl-3(tri-fluoromethyl) benzeneethane mine hydrochloride	5 mg/kg daily	
A44			selective serotonin reuptake inhibitors			
A45			enterostatin agonist			
A46			galanin antagonist			
A47			urocortin agonist			
A48			CCK agonist			
A49			UCP activating agents			
A50	ergoset					
A51	fluoxetine hydrochloride	Prozac				

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A52	fluvoxamine maleate	Luvox				
A53	trazodone hydrochloride	Desyrel				
A54	Dehydro-epiandrosterone					
A55	glucocorticosteroid					
A56			Prolactin modulators			U.S. Patent No. 5,744,477 to Cincotta, <i>et al.</i>
A57	citalopram	Celexa				
A58			Growth-hormone secretagogues			U.S. Patent No. 6,110,932 to Carpino, <i>et al.</i>
A59			benzazoline derivative			U.S. Patent No. 5,710,152 to Nagao, <i>et al.</i>
A60	chromium picolinate		Chromium formulations and derivatives			
A61	L-glutamine					
A62	caffeine					
A63	methamphetamine	Desoxyn				

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
	hydrochloride					
A64	benzphetamine hydrochloride	Didrex				
A65	sumatriptan succinate	Imitrex				
A66				hydroxycitric acid		
A67			Ciliary neurotropic factor			
A68	human steroidal hormone (RF1051)					
A69	cholecystokinin					
A70	bombesin					
A71	glucagon					
A72	insulin					
A73	cyclohistidyl-proline					
A74	somatomedin					
A75			selective CRF agonist			
A76	apoprotein IV					

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A77			α 1-adrenergic receptor agonists			
A78			antihistamine			
A79	digitalis					
A80	thyroid hormone					
			5-HT _{2c} agonists			WO-A-98/30548; EP-A-0655440; CA-2132887; and CA-2153937
A81			5-HT _{2A} agonist			
A82				(R)-N-4-2-2-Hydroxy-2-(pyridin-3-yl)ethylaminoethyl-phenyl-4-(3-cyclopentylpropyl)-5-tetrazolon-1-ylbenzenesulfonamide		WO 95/29159 and U.S. Pat. No. 5,561,142

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A83			Dopamine antagonist			
A84		Zymax				
A85		lonamin				
A86	diazoxide	Proglycem				
A87	naltrexone	Revia				
A88	5-hydroxy tryptophan					
A89	hypericum					
A90			Adipocyte complement-related protein (Acrp30) and adipocyte complement-related protein (Acrp30) modulators			
A91			Adipsin modulators			
A92	botanical P57					
A93			Cannabinoid			

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A94			antagonists			
A95			tyrosine phosphatase modulators			
A96	phytostanol		11beta hydroxysteroid dehydrogenase type 1 modulators			
A97	aminosterol					
A98	beacon					
A99	calpain 10					
A100	corticotropin releasing hormone					
A101			Cyclic AMP response element-binding protein modulators			
A102			Diacylglycerol o-acetyltransferase			

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A103			modulators Fatty acid transport protein 4 modulators			
A104	follistatin					
A105	GATA					
A106			G protein beta-3 subunit 825T modulator			
A107			Ghrelin receptor antagonists			
A108			High mobility group 1C modulator			
A109			Kalikrein modulators			
A110			Melanin-concentrating hormone receptor modulators			
A111	oleylethanolamide					
A112			Perilipin			

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
			modulators			
			Tub gene modulators			
A113	Desmethyl-sibutramine					
A114	agouti protein					
A115			Anticonvulsants			
A116			Leptin receptor modulators			
A117	eltroxin					
A118	levothroid					
A119	tertroxin					
A120	synthroid					
A121	lonamin					
A122	phen-fen					
A123	eltroxin					
A124	cyronine					
A125	asenlix					
A126			Metabolic accelerators			
A127			Adipogenesis modulating			

Table 3: Weight-loss Agents

Number	Generic Name	Trade Name(s)	Drug Class	Compound Name	Dose	Reference
A128			agents			
			Pyrroloquinolines			U.S. Patent No. 6,365,598 Adams, <i>et al.</i>
A129			NK-1 receptor antagonists			EP No. 0 577 394
A130	bisphenol A diglycidyl ether		PPAR-gamma antagonist			U. S. Patent No. 6,033,656 to Mikami, <i>et al.</i>
A131			PPAR-alpha agonists			U.S. Patent No. 6,028,109 to Willson
A132			Leptin agonists			

5 [000213] As described above, several weight-loss agents are available for the treatment or prevention of obesity, obesity-related complications and for causing weight-loss. The majority of available weight-loss agents are "anorectic(s)" or appetite-suppressant medications. Appetite-suppressant medications promote weight loss by decreasing appetite or increasing the feeling or sensation of being full. These medications decrease appetite by increasing levels of serotonin or catecholamine--two brain chemicals that affect mood and appetite. Preferred weight-loss agents include anorectic compounds that cause weight-loss through the suppression of a subject's appetite, which causes a reduction in the number of calories consumed.

15 [000214] Other preferred weight-loss agents effectuate weight-loss through molecular mechanisms via modulation of the process of adipogenesis (*i.e.* adipogenesis modulating agents). Slowing or halting adipogenesis will reduce the number and/or size of adipocytes or fat cells. Accordingly, the reduction in number or size of adipocytes will result in a subject's loss of weight.

20 [000215] As used herein, the term "adipogenesis modulating" means the interference at any point, or more than one point, within the natural (normally occurring) process of differentiation of a mesenchymal cell into a pre-adipocyte cell and then into a fully mature adipocyte. The terms "adipogenesis modulating" and "modulating adipogenesis", which may be used interchangeably herein, include either a decrease in the number of mature adipocytes or a decrease in the size of mature adipocytes. The term "adipogenesis modulating" also includes halting or suppressing further differentiation or development within the adipogenesis process. In some instances, modulating adipogenesis also includes increasing either the size or number of adipocytes. Thus, any departure from the natural process in the development of a mature adipocyte is encompassed by the term "adipogenesis modulating".

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[000216] Examples of such agents capable of modulating adipogenesis include, but are not limited to, "PPAR-gamma antagonists", which modulate the process of adipogenesis by antagonism of the PPAR-gamma receptor itself or by down-regulation of PPAR-gamma receptor mRNA synthesis. As used herein, the term "mRNA" refers to messenger RNA.
5 For example, U.S. Patent No. 6,033,656 to Mikami, *et al.* provides methods of suppressing the activation of PPAR-gamma in a mammalian body by administering to a subject in need of such therapy, an effective amount of the compound, bisphenol A diglycidyl ether.

10 [000217] Still other preferred weight-loss agents cause weight-loss by increasing the basal rate of metabolism in a subject (*i.e.* "metabolic accelerators"). These agents cause a subject to metabolically expend more calories than are ingested, thus, resulting in weight-loss. Metabolic accelerators have been used heretofore for drug therapies of obesity. For
15 example, androgens such as dehydroepiandrosterone are known to have anti-obesity action (Japanese Patent Unexamined Publication No. (Hei)2-275895/1990). Such androgens are believed to activate intramuscular anabolism to induce the consumption of stored fat.

[000218] Therefore, in a preferred embodiment, the weight-loss agent is
20 any compound capable of having any effect on a subject's weight through appetite suppression or by increasing the rate of metabolism, including compounds capable of modulating the process of adipogenesis *in vivo* or *in vitro*, but the weight-loss agent does not include compounds that are Cox-2 inhibitors.

25 [000219] More preferred is that the weight-loss agent comprises any of one or more agents selected from anorectics, serotonin reuptake inhibitors, serotonin releasing agents, activators of ATP-dependent K⁺ channels, anti-hyperglycemics, amphetamines and amphetamine derivatives, melanocortin-4 receptor agonists, neuropeptide Y antagonists,
30 lipase inhibitors, beta(3)-adrenergic agonists, glucagon-like peptide-1 agonists, PPAR-gamma antagonists, PPAR-gamma partial agonists, orexins, enterostatin agonists, galanin antagonists, urocortin agonists,

CCK agonists, UCP activating agents, prolactin modulators, growth-
 hormone secretagogues, benzoazine derivatives, ciliary neurotropic factor,
 selective CRF agonists, $\alpha 1$ -adrenergic receptor agonists, antihistamines,
 5-HT_{2C} agonists, 5-HT_{2A} agonists, catecholamine modulators, chromium
 5 formulations and derivatives, dopamine antagonists, adipocyte
 complement-related protein (Acrp30), adipocyte complement-related
 protein (Acrp30) modulators, adipsin modulators, cannabinoid antagonists,
 tyrosine phosphatase modulators, 11 β hydroxysteroid dehydrogenase
 type 1 modulators, cyclic AMP response element-binding protein
 10 modulators, diacylglycerol o-acyltransferase modulators,
 dehydroepiandrosterone derivatives, fatty acid transport protein 4
 modulators, G protein beta-3 subunit 825T modulator, high mobility group
 1C modulator, kallikrein modulators, melanin-concentrating hormone
 receptor modulators, perilipin modulators, tub gene modulators, alpha-
 15 adrenergic agonists, beta-adrenergic agonists, anticonvulsants, leptin
 receptor modulators, metabolic accelerators, adipogenesis modulating
 agents, pyrroloquinolines, NK-1 receptor antagonists, PPAR-alpha
 agonists, ghrelin receptor antagonists, leptin agonists, histamine-3
 antagonists, and mixtures thereof.

20 **[000220]** Even more preferred is that the weight-loss agent comprises
 any one or more of the weight-loss treatment agents selected from group
 consisting of phentermine, diethylpropion, mazindol, phendimetrazine,
 benzphetamine, sibutramine, orlistat, fenfluramine, dexfenfluramine,
 bupropion, diazoxide, diethylpropion, metformin, sertraline, topiramate,
 25 (+)norfenfluramine, leptin derivatives and formulations, rimonabant,
 aminorex, adiponectin, phenylpropanolamine, amantadine, nizatidine,
 cimetidine, amphetamine, dinitrophenol, dehydroepiandrosterone,
 mazindol benzphetamine, phendimetrazine, phentermine,
 dexfenfluramine, amylin, mazindol, ephedrine, fenfluramine, ergoset,
 30 fluoxetine hydrochloride, fluvoxamine maleate, trazodone hydrochloride,
 dehydroepiandrosterone, glucocorticosteroid, citalopram, chromium
 picolinate, L-glutamine, caffeine, methamphetamine hydrochloride,

benzphetamine hydrochloride, sumatriptan succinate, human steroidal hormone (RF1051), cholecystokinin, bombesin, glucagon, insulin, cyclohistidyl-proline, somatomedin, apoprotein IV, digitalis, thyroid hormone, diazoxide, naltrexone, 5-hydroxy tryptophan, hypericum, botanical P57, phytostanol, aminosterol, beacon, calpain 10, corticotropin releasing hormone, follistatin, GATA, oleylethanolamide, agouti protein, eltroxin, levothroid, tertroxin, synthroid, lonamin, phen-fen, eltroxin, cyronine, asenlix, bisphenol A diglycidyl ether, desmethyisibutramine, and mixtures thereof.

10 **[000221]** More preferred still is that the weight-loss agent comprises any of one or more agents selected from the following classes of weight-loss treatment agents including anorectics, metabolic accelerators, lipase inhibitors, serotonin uptake inhibitors, adipocyte complement-related protein (Acrp30), adipocyte complement-related protein (Acrp30)

15 modulators, serotonin release agents, catecholamine modulators, PPAR-gamma antagonists, PPAR-gamma partial agonists, and mixtures thereof.

[000222] More preferred is that the weight-loss agent is selected from the group consisting of anorectics, adipocyte complement-related protein (Acrp30) modulators, metabolic accelerators, PPAR-gamma antagonists, 20 PPAR-gamma partial agonist classes of weight-loss agents, and mixtures thereof.

[000223] Even more preferred still is that the weight-loss agent comprises sibutramine or orlistat.

[000224] Any combination of the Cox-2 inhibitors and weight-loss 25 agents that are described above can be used in the novel composition and the novel pharmaceutical composition. In one embodiment, one or more of an anorectic class of weight-loss agent is combined with at least one Cox-2 inhibitor. In another embodiment, one or more of an adipogenesis modulating agent (e.g., PPAR gamma antagonists or partial agonists) is 30 combined with at least one Cox-2 inhibitor. In still another embodiment, one or more metabolism modulating agents are combined with at least one Cox-2 inhibitor. Further encompassed by the present invention are any

combinations of anorectics, adipogenesis modulating agents, and metabolism modulating agents each independently, or any combinations thereof, are also combined with at least one Cox-2 inhibitor.

5 [000225] Thus, in a preferred embodiment, a Cox-2 inhibitor such as, for example, celecoxib can be combined with any combination of anorectics, adipogenesis modulating agents, or metabolism modulating agents, each independently or any combinations thereof. For example, a Cox-2 inhibitor such as, celecoxib, can be combined with any of the aforementioned weight-loss agents cited in Table 3, such as sibutramine.

10 [000226] In a preferred embodiment, the present invention encompasses a therapeutic composition comprising a Cox-2 inhibitor and a weight-loss agent.

15 [000227] Cox-2 inhibitors and weight-loss agents that are useful in the present invention can be of any purity or grade, as long as the preparation is of a quality suitable for pharmaceutical use. The Cox-2 inhibitors and weight-loss agents can be provided in pure form, or it can be accompanied with impurities or commonly associated compounds that do not affect its physiological activity or safety. The Cox-2 inhibitors and weight-loss agents can also be supplied in the form of a prodrug, an isomer, a tautomer, a racemic mixture, or in any other chemical form or combination that, under physiological conditions, still provides for inhibition of the Cox-2 enzyme.

20 [000228] The compositions of the present invention can comprise a Cox-2 inhibitor and a weight-loss agent as an active ingredient or a pharmaceutically acceptable salt, thereof, and also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients.

25 [000229] The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, 30

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5 fumaric, pyruvic, aspartic, glutamic, benzoic, hydrochloric, trifluoroacetic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, β -hydroxybutyric, galactaric and galacturonic acids.

10 **[000230]** Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts.

15 **[000231]** Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, 20 methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

25 **[000232]** Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to, appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences.

30 **[000233]** Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N, N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and

procaine. Exemplary pharmaceutically acceptable acids include, without limitation, hydrochloric acid, hydroiodic acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid, oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[000234] All of the above salts and ions can be prepared by those skilled in the art by conventional means from the corresponding compounds of the present invention.

[000235] In the present invention, a Cox-2 inhibitor and/or weight-loss agent are administered to a patient in need of such treatment or prevention according to standard routes of drug delivery that are well known to one of ordinary skill in the art. The particular route and dosage of the Cox-2 inhibitor and the weight-loss agent depend upon the needs of the subject being treated, the type of treatment or prevention, the efficacy of the compound and the degree of disease severity in the subject.

[000236] The combination of a Cox-2 inhibitor and a weight-loss agent can be provided in a pharmaceutically acceptable carrier or excipient to form a pharmaceutical composition. In a preferred embodiment, the present invention encompasses a pharmaceutical composition comprising a Cox-2 inhibitor, a weight-loss agent, and a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable" is used herein to mean that the modified noun is appropriate for use in a pharmaceutical product.

[000237] The compositions of the present invention may be administered enterally and/or parenterally. Oral (intra-gastric) is a preferred route of administration. Pharmaceutically acceptable carriers can be in solid dosage forms for the methods of the present invention, which include tablets, capsules, pills, and granules, which can be prepared with coatings and shells, such as enteric coatings and others well known in the art. Liquid dosage forms for oral administration include

pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs.

5 [000238] Enteral administration includes solution, tablets, sustained release capsules, enteric-coated capsules, and syrups. When administered, the pharmaceutical composition may be at or near body temperature.

10 [000239] Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations.

15 [000240] Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate, granulating and disintegrating agents, for example, maize starch, or alginic acid, binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, 20 stearic acid, or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

25 [000241] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are present as such, or mixed with water or an oil medium, for example, peanut oil, liquid 30 paraffin, or olive oil.

[000242] Aqueous suspensions can be produced that contain the active materials in a mixture with excipients suitable for the manufacture of

aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-
5 occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and
10 a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

[000243] The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate, one or
15 more coloring agents, one or more flavoring agents, or one or more sweetening agents, such as sucrose or saccharin.

[000244] Oily suspensions may be formulated by suspending the active ingredients in an omega-3 fatty acid, a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid
20 paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol.

[000245] Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant
25 such as ascorbic acid.

[000246] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting
30 agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[000247] Syrups and elixirs containing the Cox-2 inhibitor and/or weight-loss agent may be formulated with sweetening agents, for example glycerol, sorbitol, or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

5 **[000248]** The subject method of prescribing a Cox-2 inhibitor and/or weight-loss agent and compositions comprising the same can also be administered parenterally, either subcutaneously, or intravenously, or intramuscularly, or intrasternally, or by infusion techniques, in the form of sterile injectable aqueous or olagenous suspensions. Parenteral
10 administration includes subcutaneous, intramuscular, intradermal, intramammary, intravenous, and other administrative methods known in the art.

[000249] Such suspensions may be formulated according to the known art using those suitable dispersing of wetting agents and suspending
15 agents, which have been mentioned above or other acceptable agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and
20 isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, n-3 polyunsaturated fatty acids may find use in the preparation of injectables.

25 **[000250]** Administration of either one or both of the Cox-2 inhibitor and weight-loss agents can also be by inhalation, in the form of aerosols or solutions for nebulizers. Therefore, in one embodiment, the Cox-2 inhibitor and/or the weight-loss agent is administered by direct inhalation into the respiratory system of a subject for delivery as a mist or other
30 aerosol or dry powder. Delivery of drugs or other active ingredients directly to the subject's lungs provides numerous advantages including, providing an extensive surface area for drug absorption, direct delivery of

therapeutic agents to the disease site in the case of regional drug therapy, eliminating the possibility of drug degradation in the subject's intestinal tract (a risk associated with oral administration), and eliminating the need for repeated subcutaneous injections.

5 [000251] Aerosols of liquid particles comprising the active materials may be produced by any suitable means, such as inhalatory delivery systems. Nebulizers are commercially available devices which transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist
10 either by means of acceleration of compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers consist of the active ingredient in a liquid carrier. The carrier is typically water, and most preferably sterile, pyrogen-free water, or a dilute aqueous alcoholic solution,
15 preferably made isotonic, but may be hypertonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives if the formulation is not made sterile, for example, methyl hydroxybenzoate, as well as antioxidants, flavoring agents, volatile oils, buffering agents and surfactants, which are normally used in the preparation of pharmaceutical compositions.

20 [000252] Aerosols of solid particles comprising the active materials may likewise be produced with any solid particulate medicament aerosol generator. Aerosol generators for administering solid particulate medicaments to a subject produce particles which are respirable, as explained above, and generate a volume of aerosol containing a
25 predetermined metered dose of a medicament at a rate suitable for human administration.

[000253] One type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely
30 comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the powder is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened *in situ* and the powder

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delivered by means of air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active materials, a suitable powder diluent, such as lactose, and an optional surfactant.

[000254] A second type of aerosol generator is a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the Cox-2 inhibitor and/or the weight-loss agent in a liquified propellant. During use, the metered dose inhaler discharges the formulation through a valve, adapted to deliver a metered volume, to produce a fine particle spray containing the active materials. Any propellant may be used for aerosol delivery, including both chlorofluorocarbon-containing propellants and non-chlorofluorocarbon-containing propellants.

[000255] A third type of aerosol generator is an electrohydrodynamic (EHD) aerosol generating device, which has the advantage of being adjustable to create substantially monomodal aerosols having particles more uniform in size than aerosols generated by other devices or methods. Typical EHD devices include a spray nozzle in fluid communication with a source of liquid to be aerosolized, at least one discharge electrode, a first voltage source for maintaining the spray nozzle at a negative (or positive) potential relative to the potential of the discharge electrode, and a second voltage source for maintaining the discharge electrode at a positive (or negative) potential relative to the potential of the spray nozzle.

[000256] Most EHD devices create aerosols by causing a liquid to form droplets that enter a region of high electric field strength. The electric field then imparts a net electric charge to these droplets, and this net electric charge tends to remain on the surface of the droplet. The repelling force of the charge on the surface of the droplet balances against the surface tension of the liquid in the droplet, thereby causing the droplet to form a cone-like structure known as a Taylor Cone. In the tip of this cone-like

structure, the electric force exerted on the surface of the droplet overcomes the surface tension of the liquid, thereby generating a stream of liquid that disperses into a many smaller droplets of roughly the same size. These smaller droplets form a mist which constitutes the aerosol cloud that the user ultimately inhales.

[000257] In a preferred embodiment, the administration of the compositions of the present invention can also be by a rectal route of delivery. Rectal routes of delivery are in the form of suppositories prepared by mixing the drug with a suitable non-irritating excipient, which is solid at ordinary temperature, but liquid at the rectal temperature and will therefore, melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[000258] Also encompassed by the present invention is buccal or "sub-lingual" administration, which includes lozenges or a chewable gum comprising the compounds, set forth herein. The compounds can be deposited in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compounds in an inert base such as gelatin and glycerin or sucrose and acacia.

[000259] The present invention further encompasses intranasal administration comprising the compounds set forth herein. Intranasal dosage forms include, but are not limited to, aerosols, drops, gels, powders, and mixtures thereof.

[000260] Other methods for administration of the Cox-2 inhibitor compound and/or the weight-loss agent include dermal patches that release the medicaments directly into a subject's skin.

[000261] Topical delivery systems are also encompassed by the present invention and include ointments, powders, sprays, creams, jellies, collyriums, solutions or suspensions.

[000262] The compositions of the present invention can optionally be supplemented with additional agents such as, for example, viscosity enhancers, preservatives, surfactants and penetration enhancers.

5 [000263] Viscosity is an important attribute of many medications. Drops that have a high viscosity tend to stay in the body for longer periods and thus, increase absorption of the active compounds by the target tissues or increase the retention time. Such viscosity-building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methylcellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art. Such agents are typically employed at a level of from 0.01% to 2% by weight.

10 [000264] Preservatives are optionally employed to prevent microbial contamination during use. Suitable preservatives include polyquaternium-1, benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, or other agents known to those skilled in the art. The use of polyquaternium-15 1 as the antimicrobial preservative is preferred. Typically, such preservatives are employed at a level of from 0.001% to 1.0% by weight.

20 [000265] The solubility of the components of the present compositions may be enhanced by a surfactant or other appropriate co-solvent in the composition. Such co-solvents include polysorbate 20, 60, and 80, polyoxyethylene/polyoxypropylene surfactants (e.g. Pluronic F-68, F-84 and P-103), cyclodextrin, or other agents known to those skilled in the art. Typically, such co-solvents are employed at a level of from 0.01% to 2% by weight.

25 [000266] A penetration enhancer is an agent used to increase the permeability of the skin to an active agent to increase the rate at which the drug diffuses through the skin and enters the tissues and bloodstream. Thus, in one embodiment of the present invention, a penetration enhancer may be added to a Cox-2 inhibitor topical composition or a Cox-2 inhibitor and weight-loss agent topical composition.

30 [000267] Examples of penetration enhancers suitable for use with the compositions of the present invention include: alcohols, such as ethanol and isopropanol; polyols, such as n-alkanols, limonene, terpenes,

dioxolane, propylene glycol, ethylene glycol, other glycols, and glycerol; sulfoxides, such as dimethylsulfoxide (DMSO), dimethylformamide, methyl dodecyl sulfoxide, dimethylacetamide; esters, such as isopropyl myristate/palmitate, ethyl acetate, butyl acetate, methyl propionate, and capric/caprylic triglycerides; ketones; amides, such as acetamides; oleates, such as triolein; various surfactants, such as sodium lauryl sulfate; various alkanolic acids, such as caprylic acid; lactam compounds, such as azone; alkanols, such as oleyl alcohol; dialkylamino acetates, and admixtures thereof.

10 [000268] Pharmaceutically acceptable excipients and carriers encompass all the foregoing and the like. The above considerations concerning effective formulations and administration procedures are well known in the art and are described in standard textbooks. *See e.g.* Gennaro, A. R., Remington: The Science and Practice of Pharmacy, 20th Edition, (Lippincott, Williams and Wilkins), 2000; Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania, 1975; Liberman, *et al.*, Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe, *et al.*, Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American
15 Pharmaceutical Association, Washington, 1999.

20 [000269] In other preferred embodiments, the present invention encompasses a kit for preventing or treating obesity or an obesity-related complication in a subject that is in need of such prevention or treatment, the kit comprising one dosage form comprising a Cox-2 inhibitor and a
25 second dosage form comprising a weight-loss agent.

[000270] It will be appreciated that the amount of the Cox-2 inhibitor and the weight-loss agent required for use in the treatment or prevention of obesity and obesity-related complications will vary depending upon the particular compounds or compositions selected.

30 [000271] Daily dosages can vary within wide limits and will be adjusted to the individual requirements in each particular case. In general, for administration to adults, an appropriate daily dosage is described herein,

although the limits that are identified as being preferred may be exceeded if expedient. The daily dosage can be administered as a single dosage or in divided dosages. Various delivery systems include capsules, tablets, food, chewing gum, lozenges, dermal patches, and gelatin capsules, for example.

[000272] The appropriate dosage level of a Cox-2 inhibitor will generally be from about 0.01 mg per kg to about 140 mg per kg subject body weight per day, which may be administered in single or multiple doses.

Preferably, the dosage level will be about 0.1 mg/kg to about 25 mg/kg per day; more preferably about 0.5 mg to about 10 mg/kg per day.

[000273] In larger mammals, for example humans, a typical indicated dose is about 0.5 mg to 7 grams orally per day. A compound may be administered on a regimen of several times per day, for example 1 to 4 times per day, preferably once or twice per day.

[000274] The amount of the Cox-2 inhibitor that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 7 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms for the Cox-2 inhibitor will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

[000275] The dosage level of a weight-loss agent will necessarily depend on the particular agent that is used. However, in general, the appropriate dosage level of a weight-loss agent will generally be from about 0.002 mg per kg to about 10 mg per kg subject body weight per day, which may be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 mg/kg to about 7 mg/kg per day; more preferably about 0.1 mg to about 5 mg/kg per day.

[000276] The exact dosage and regimen for administering a Cox-2 inhibitor alone or in combination with a weight-loss agent will necessarily depend upon the potency and duration of action of the compounds used, the nature and severity of the illness to be treated, as well as the sex, age, weight, general health and individual responsiveness of the patient to be treated, and other relevant circumstances. Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711.

[000277] To determine the effectiveness of a particular dosage of a Cox-2 inhibitor alone or in combination with a weight-loss agent, desirable weight standards are derived by comparing a particular subject's weight to a mathematical formula known as Body Mass Index (BMI), which represents weight levels associated with the lowest overall risk to health. See e.g. Garrow JS and Webster J. Quetelet's index (W/H^2) as a measure of fatness, *International Journal of Obesity* 9:147-153 (1985); Gallagher D, et al. How useful is BMI for comparison of body fatness across age, sex and ethnic groups? *American Journal of Epidemiology* 143:228-239 (1996); Willett W, et al. Guidelines for healthy weight. *New England Journal of Medicine* 341:427-434 (1999); World Health Organization. Physical status: The use and interpretation of anthropometry. Geneva, Switzerland: World Health Organization. *WHO Technical Report Series* (1995); Calle EE, et al. BMI and mortality in a prospective cohort of U.S. adults. *New England Journal of Medicine* 341:1097-1105 (1999).

[000278] Where BMI is utilized as a measure of weight, an individual is considered overweight when BMI values range between 25.0 and 29.9. Obesity is defined for BMI values of greater than or equal to 30.0. For example, the World Health Organization assigns BMI values as follows: 25.0-29.9, Grade I obesity (moderately overweight); 30-39.9, Grade II obesity (severely overweight); and 40.0 or greater, Grade III obesity (massive/morbid obesity). Using weight tables, obesity is classified as mild (20-40% overweight), moderate (41-100% overweight), and severe

(>100%) overweight. Thus, individuals 20% over ideal weight guidelines are considered obese. Individuals 1-19.9% over ideal weight are classified as overweight.

[000279] Another way to determine the effectiveness of a particular dosage of a Cox-2 inhibitor alone or in combination with a weight-loss agent is to observe or measure its effect upon the process of adipogenesis or upon an adipogenesis-related disorder. This may be achieved by any of the techniques known to those practiced in the art of measuring lean vs. fat body mass composition.

[000280] The term "adipogenesis" refers, in a general sense to the process by which undifferentiated precursor cells differentiate into fat cells. Specifically, adipogenesis is a physiological developmental process by which an undifferentiated mesenchymal cell differentiates into a pre-adipocyte cell, which then undergoes a secondary differentiation step to become a lipid-filled mature adipocyte. Thus, the term adipogenesis is meant to encompass the entire developmental process from undifferentiated mesenchymal cell to a fully developed and mature adipocyte cell. As used herein, the terms "adipogenesis-related disorder" refers to any physiological condition in a subject wherein the normal process of adipogenesis has been altered. For example, where the process of adipogenesis occurs too frequently or too excessively, it can result in the physiological condition of obesity.

[000281] Several protocols have been reported for observing and measuring the effect of a given compound or treatment or therapy upon adipogenesis or pre-adipocyte differentiation. See e.g. Abbott, D., *et al.*, *J. Biol. Chem.* 272(51):32454-32462 (1997); Gregoire, F., *et al.*, *Physiolog. Reviews* 78(3):783-809 (1998); Kelly, K., *et al.*, *Endocrinology* 139(5):2622-2628 (1998); Fowler, S., *et al.*, *J. Histochem. Cytochem.* 33:833-836 (1985); and Greenspan, P., *et al.*, *J. Cell. Biol.* 100:965-972 (1985).

[000282] As used herein, the term "subject" for purposes of treatment includes any subject, and preferably is a subject who is in need of the

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prevention and/or treatment of obesity, or who has weight-related disorder or a weight-related or obesity complication. The subject is typically an animal, and yet more typically is a mammal. "Mammal", as that term is used herein, refers to any animal classified as a mammal, including

5 humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cattle, etc. Preferably, the mammal is a human.

For methods of prevention, the subject is any subject, and preferably is a subject that is in need of prevention and/or treatment of obesity or a weight-related disorder or an obesity-related complication. Veterinary use
10 for weight reduction of domestic animals or food production uses of this therapy to improve fat/muscle ratios and thus, food taste and quality are also encompassed by the present invention.

[000283] As used herein, the terms "subject is in need of the prevention or treatment of obesity or an obesity-related complication" refer to any
15 subject who is suffering from or is predisposed to obesity or any obesity-related complication described herein. Also, the terms "subject is in need of the prevention or treatment of obesity or an obesity-related complication" refer to any subject who desires to lose weight and is not necessarily suffering from obesity or being overweight or suffering from a
20 obesity-related disorder. Thus, any subject who desires to lose any amount of weight is encompassed by the terms "subject is in need of the prevention or treatment of obesity or an obesity-related complication".

[000284] The terms "subject is in need of the prevention or treatment of obesity or an obesity-related complication" also refer to any subject that
25 requires a lower dose of weight-loss agents. In addition, the terms "subject is in need of the prevention or treatment of obesity or an obesity-related complication" means any subject who requires a reduction in the side-effects of a weight-loss agent. Furthermore, the terms "subject is in need of the prevention or treatment of obesity or an obesity-related
30 complication" means any subject who requires improved tolerability to any weight-loss agent for obesity therapy. Finally, the terms "subject is in need of the prevention or treatment of obesity or an obesity-related

complication" means any subject who requires or desires the physiological modulation of the process of adipogenesis.

[000285] The present invention also encompasses the therapeutic treatment and prevention of several obesity-related complications.

5 According to the NIH Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, all adults (aged 18 years or older) who have a BMI of 25 or more are considered at risk for premature death and disability as a consequence of overweight and obesity. These health risks increase even more as the severity of a
10 subject's obesity increases.

[000286] Therefore, the present invention encompasses the treatment and prevention of situations where the subject is obese and suffers from or is predisposed to one or more obesity-related complications selected from the group consisting of high blood pressure, hypertension, high blood
15 cholesterol, dyslipidemia, type 2 diabetes, Insulin resistance, glucose intolerance, hyperinsulinemia, coronary heart disease, cardiovascular disease, angina pectoris, congestive heart failure, stroke, gallstones, cholecystitis, cholelithiasis, gout, osteoarthritis, rheumatoid arthritis, obstructive sleep apnea, respiratory problems, cancer (such as
20 endometrial, breast, prostate and colon cancers), complications of pregnancy, poor female reproductive health irregularities (such as menstrual irregularities, infertility and irregular ovulation); bladder control problems (such as stress incontinence), uric acid nephrolithiasis, psychological disorders (such as depression, eating disorders, distorted
25 body image and low self esteem), coronary heart disease, atherosclerotic diseases, arteriosclerosis, stable angina, unstable angina, type II diabetes, sleep apnea, high LDL cholesterol, low HDL cholesterol, high triglycerides, high blood glucose and including any other disorders or complications that are amenable to amelioration through inhibition of the
30 Cox-2 enzyme alone or in combination with administration to a subject in need of such treatment of an effective amount of the weight-loss agents referred to herein.

5 [000287] More preferred is where the subject is obese and suffers from or is predisposed to one or more obesity-related complications selected from the group consisting of rheumatoid arthritis, arteriosclerosis, stable angina, unstable angina, hypertension, dyslipidemia, type 2 diabetes, stroke, gallbladder disease, cardiovascular disease, osteoarthritis, hypercholesterolemia, sleep apnea, respiratory problems, cancer and stroke.

10 [000288] Even more preferred is where the subject is obese and suffers from or is predisposed to one or more obesity-related complications selected from the group consisting of cardiovascular disease, osteoarthritis, rheumatoid arthritis, arteriosclerosis, stable angina, unstable angina, hypertension and hypercholesterolemia.

15 [000289] Still further preferred is where the subject is obese and suffers from or is predisposed to one or more obesity-related complications selected from the group consisting of cardiovascular disease, osteoarthritis, rheumatoid arthritis, arteriosclerosis, stable angina and unstable angina.

20 [000290] Preferably, the present invention also encompasses the treatment and prevention of obesity and obesity-related complications and provides methods and compositions for causing weight-loss in a subject that desires to lose weight.

25 [000291] The methods and compositions of the present invention not only encompass the prevention or treatment of obesity and obesity-related disorders in humans, but also in several animals. For example, many animals also suffer adverse consequences related to obesity. Obese cats and dogs have a greater risk for diseases including osteoarthritis, ligament injuries, perineal dermatitis, diabetes mellitus, cardiomyopathy, and urologic syndrome. Therefore, the methods and compositions of the present invention are useful to maintain a healthy weight in family pets in order to minimize disease risk. See U.S. Patent No. 6,071,544 to Sunvold.

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[000292] Accordingly, besides being useful for humans, the methods and compositions of the present invention also encompass the treatment

and prevention of obesity and obesity-related disorders in other mammals, including horses, dogs, cats, rats, mice, sheep, pigs, cattle, hamsters, gerbils, and the like.

5 [000293] The following examples describe embodiments of the invention. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, together with the examples, be considered to be exemplary only, with the scope and spirit of the invention being indicated by the
10 claims which follow the examples. In the examples, all percentages are given on a weight basis unless otherwise indicated.

EXAMPLE 1

[000294] This example illustrates the preparation of the Cox-2 inhibitor, celecoxib.

15 [000295] Step 1: Preparation of 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione.

[000296] Following the disclosure provided in U.S. Patent No. 5,760,068, 4'-Methylacetophenone (5.26 g, 39.2 mmol) was dissolved in 25 mL of methanol under argon and 12 mL (52.5 mmol) sodium methoxide
20 in methanol (25%) was added. The mixture was stirred for 5 minutes and 5.5 mL (46.2 mmol) ethyl trifluoroacetate was added. After refluxing for 24 hours, the mixture was cooled to room temperature and concentrated. 100 mL 10% HCl was added and the mixture extracted with 4 x 75 mL ethyl acetate. The extracts were dried over MgSO₄, filtered and
25 concentrated to afford 8.47 g (94%) of a brown oil which was carried on without further purification.

[000297] Step 2: Preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

30 [000298] To the dione from Step 1 (4.14 g, 18.0 mmol) in 75 mL absolute ethanol, 4.26 g (19.0 mmol) 4-sulphonamidophenylhydrazine hydrochloride was added. The reaction was refluxed under argon for 24 hours. After cooling to room temperature and filtering, the reaction mixture

was concentrated to afford 6.13 g of an orange solid. The solid was recrystallized from methylene chloride/hexane to give 3.11 g (8.2 mmol, 46%) of the product as a pale yellow solid, having a melting point (mp) of 157°-159°C; and a calculated composition of C₁₇ H₁₄ N₃ O₂ SF₃; C, 53.54; 5 H, 3.70; N, 11.02. The composition that was found by analysis was: C, 53.17; H, 3.81; N, 10.90.

EXAMPLE 2

10 [000299] This illustrates the production of a composition containing the Cox-2 inhibitor, celecoxib and the weight-loss agent, sibutramine, and of a pharmaceutical composition containing the combination.

15 [000300] Sibutramine may be synthesized by following the procedures of U.S. Patent Nos. 4,746,680; 4,929,629; or 5,436,272 or it may be supplied by any one of several commercially available preparations. One such preparation can be obtained under the trade name Meridia® from Abbott Laboratories, North Chicago, IL.

[000301] Each caplet of Meridia® contains 10 mg of sibutramine.

[000302] Celecoxib can be prepared as described in Example 1, or it can be obtained under the trade name Celebrex® from Pharmacia Corporation, Peapack, NJ.

20 [000303] A therapeutic composition of the present invention can be formed by intermixing sibutramine, 10 g; and 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (200 g, as produced in Example 1, or as available from Pharmacia Corporation, Peapack, NJ, under the tradename Celebrex®), in a suspension or solution with a sterile 25 pharmaceutically acceptable liquid.

[000304] After mixing, the combination of sibutramine and celecoxib forms a therapeutic composition that is sufficient for the production of about 1000 human single dose units. Each single dose unit contains about 10 mg of loperamide HCl and about 200 mg of celecoxib.

30 [000305] If desirable, a solid carrier and other materials may be intermixed with the therapeutic composition to form a pharmaceutical composition and the resulting pharmaceutical composition may be formed

into capsules for human consumption, for example, by conventional capsule-forming equipment, where each capsule contains can contain about the same amount of the active ingredients as each of the single dose units of the liquid preparation described above.

5 [000306] All references cited in this specification, including without limitation all papers, publications, patents, patent applications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles, periodicals, and the like, are hereby incorporated by reference into this specification in their entirety. The discussion of the
10 references herein is intended merely to summarize the assertions made by their authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinency of the cited references.

[000307] In view of the above, it will be seen that the several
15 advantages of the invention are achieved and other advantageous results obtained.

[000308] As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is
20 intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

WHAT IS CLAIMED IS:

1. A method of preventing or treating obesity and obesity-related complications in a subject comprising administering to the subject a Cox-2 inhibitor.
2. The method according to claim 1, wherein the Cox-2 inhibitor is administered to the subject in combination with one or more weight-loss agents.
3. The method according to claim 1 or 2, wherein the Cox-2 inhibitor comprises a Cox-2 selective inhibitor.
4. The method according to claim 3, wherein the Cox-2 selective inhibitor comprises at least one compound that is selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, etoricoxib, meloxicam, rofecoxib, lumiracoxib, prodrugs of any of them, and mixtures thereof.
5. The method according to claim 3, wherein the Cox-2 selective inhibitor comprises celecoxib.
6. The method according to claim 3, wherein the Cox-2 selective inhibitor comprises a chromene Cox-2 selective inhibitor.
7. The method according to claim 6, wherein the chromene Cox-2 selective inhibitor comprises at least one compound selected from the group consisting of
(S)-6-chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
(2S)-6,8-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid,
(2S)-6-chloro-8-methyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid,
(2S)-8-ethyl-6-(trifluoromethoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid,
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
(2S)-6-chloro-5,7-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, and mixtures thereof.
8. The method according to claim 2, wherein the weight-loss agent comprises at least one compound selected from the group

consisting of anorectics, serotonin reuptake inhibitors, serotonin releasing agents, activators of ATP-dependent K⁺ channels, anti-hyperglycemics, amphetamines and amphetamine derivatives, melanocortin-4 receptor agonists, neuropeptide Y antagonists, lipase inhibitors, beta(3)-adrenergic agonists, glucagon-like peptide-1 agonists, PPAR-gamma antagonists, orexins, enterostatin agonists, galanin antagonists, urocortin agonists, CCK agonists, UCP activating agents, prolactin modulators, growth-hormone secretagogues, benzoazine derivatives, ciliary neurotropic factor, selective CRF agonists, α 1-adrenergic receptor agonists, antihistamines, 5-HT_{2C} agonists, 5-HT_{2A} agonists, catecholamine modulators, chromium formulations and derivatives, dopamine antagonists, adipocyte complement-related protein (Acrp30), adipocyte complement-related protein (Acrp30) modulators, adiponin modulators, cannabinoid antagonists, tyrosine phosphatase modulators, 11 β hydroxysteroid dehydrogenase type 1 modulators, cyclic AMP response element-binding protein modulators, diacylglycerol o-acyltransferase modulators, dehydroepiandrosterone derivatives, fatty acid transport protein 4 modulators, G protein beta-3 subunit 825T modulator, high mobility group 1C modulators, kallikrein modulators, melanin-concentrating hormone receptor modulators, perilipin modulators, *tub* gene modulators, α -adrenergic agonists, beta-adrenergic agonists, anticonvulsants, leptin receptor modulators, metabolic accelerators, adipogenesis modulating agents, pyrroloquinolines, NK-1 receptor antagonists, PPAR- α agonists, ghrelin receptor antagonists, leptin agonists, histamine-3 antagonists, and mixtures thereof.

9. The method according to claim 2, wherein the weight-loss agent comprises at least one compound selected from the group consisting of phentermine, diethylpropion, mazindol, phendimetrazine, benzphetamine, sibutramine, orlistat, fenfluramine, dexfenfluramine, bupropion, diazoxide, diethylpropion, metformin, sertraline, topiramate, (+)norfenfluramine, leptin derivatives and formulations, rimonabant, aminorex, adiponectin, phenylpropanolamine, amantadine, nizatidine,

cimetidine, amphetamine, dinitrophenol, dehydroepiandrosterone, mazindol benzphetamine, phendimetrazine, phentermine, dexfenfluramine, amylin, mazindol, ephedrine, fenfluramine, ergoset, fluoxetine hydrochloride, fluvoxamine maleate, trazodone hydrochloride, dehydroepiandrosterone, glucocorticosteroid, citalopram, chromium picolinate, L-glutamine, caffeine, methamphetamine hydrochloride, benzphetamine hydrochloride, sumatriptan succinate, human steroidal hormone (RF1051), cholecystokinin, bombesin, glucagon, insulin, cyclohistidyl-proline, somatomedin, apoprotein IV, digitalis, thyroid hormone, diazoxide, naltrexone, 5-hydroxy tryptophan, hypericum, botanical P57, phytostanol, aminosterol, beacon, calpain 10, corticotropin releasing hormone, follistatin, GATA, oleylethanolamide, agouti protein, eltroxin, levothyroid, tertroxin, synthroid, lonamin, phen-fen, eltroxin, cyronine, asenlix, bisphenol A diglycidyl ether, desmethyisibutramine, prodrugs of any of them, and mixtures thereof.

10. The method according to claim 1 or 2, wherein the subject suffers from or is predisposed to obesity.

11. The method according to claim 1 or 2, wherein the subject is obese and suffers from or is predisposed to one or more obesity-related complications selected from the group consisting of high blood pressure, hypertension, high blood cholesterol, dyslipidemia, type 2 diabetes, insulin resistance, glucose intolerance, hyperinsulinemia, coronary heart disease, cardiovascular disease, hypercholesterolemia, hypertension, angina pectoris, congestive heart failure, stroke, gallbladder disease, gallstones, cholecystitis, cholelithiasis, gout, osteoarthritis, rheumatoid arthritis, obstructive sleep apnea, respiratory problems, cancer (such as endometrial, breast, prostate and colon cancers), complications of pregnancy, poor female reproductive health irregularities (such as menstrual irregularities, infertility and irregular ovulation), bladder control problems (such as stress incontinence), uric acid nephrolithiasis, psychological disorders (such as depression, eating disorders, distorted body image and low self esteem), coronary heart disease, atherosclerotic

diseases, atherosclerosis, stable angina, unstable angina, type II diabetes, high LDL cholesterol, low HDL cholesterol, high triglycerides, and high blood glucose.

12. Use of a Cox-2 inhibitor alone or in combination with a weight-loss agent for the production of a medicament for the prevention or treatment of obesity and obesity-related complications in a subject.

13. A therapeutic composition comprising a Cox-2 inhibitor and a weight-loss agent.

14. A pharmaceutical composition comprising a Cox-2 inhibitor, a weight-loss agent, and a pharmaceutically acceptable carrier.

15. A kit comprising one dosage form comprising a Cox-2 inhibitor and a second dosage form comprising a weight-loss agent.

ANEXO 2



US006159466A

United States Patent [19]**Yang et al.**[11] **Patent Number:** **6,159,466**[45] **Date of Patent:** ***Dec. 12, 2000**

[54] **AQUEOUS COMPOSITION COMPRISING
SACCHAROMYCES BOULARDII SEQUELA
AND CHROMIUM GLYCINATE
DINICOTINATE**

4,348,483	9/1982	Skogerson	435/235
4,923,855	5/1990	Jensen et al.	514/188
5,614,553	3/1997	Ashmead et al.	514/505

[75] **Inventors:** **Ping Yang**, Fullerton; **Houn Simon Hsia**, Foothill Ranch, both of Calif.

[73] **Assignee:** **Viva America Marketing, Inc.**, Costa Mesa, Calif.

[*] **Notice:** This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] **Appl. No.:** **09/015,758**

[22] **Filed:** **Jan. 29, 1998**

Related U.S. Application Data

[62] Division of application No. 08/719,572, Sep. 25, 1996.

[51] **Int. Cl.⁷** **A01N 63/04**; C12N 1/18;
C12N 1/20; A23L 1/28

[52] **U.S. Cl.** **424/93.51**; 435/255.2;
435/900; 426/62

[58] **Field of Search** 424/93.51; 426/62;
435/255.2, 940

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,343,905 8/1982 Szalay 435/256

OTHER PUBLICATIONS

Vinson et al., Nutrition Reports International, Oct. 1984, vol. 30, No. 4, pp. 911-918.

Saner et al., The American Journal of Clinical Nutrition, Oct. 1983, vol. 38, pp. 574-578.

Uusitupa et al., British Journal of Nutrition, Jul. 1992, vol. 68, No. 1, pp. 209-216.

Barnett et al. In: "Yeasts. Characterization and Identification". Cambridge University Press. Second Edition. 1990, pp. 595-597.

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[57]

ABSTRACT

The present invention includes a novel yeast strain of the genus *Saccharomyces boulardii sequela* PY31 ATCC 74366 that is able to process certain metallic compounds into biologically active forms suitable for supplementing the human diet. The present invention also includes methods for isolating such yeast, nutritional supplement compositions containing such yeast, and methods of administering the nutritional supplement compositions to humans.

4 Claims, No Drawings

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**AQUEOUS COMPOSITION COMPRISING
SACCHAROMYCES BOULARDII SEQUELA
AND CHROMIUM GLYCINATE
DINICOTINATE**

This is a divisional application of co-pending application Ser. No. 08/719,572, filed Sep. 25, 1996.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to the field of human dietary supplements, and more specifically to a novel yeast strain of the genus *Saccharomyces boulardii sequela* which has the ability to process certain metallic compounds into forms that are biologically active and useful in supplementing the human diet.

2. Background of the Invention

Metal supplementation of the human diet is generally recognized as an important area in the field of nutritional science. Although no "RDA" minimum daily intake requirements have been officially adopted, research has strongly suggested that absence of some minerals, particularly metallic minerals such as chromium, germanium, and selenium, can lead to improper functioning of the body's metabolic processes, and a host of diseases and disorders. For example, selenium has been implicated as a mineral that may affect a reduction in the incidence of certain cancers when ingested in amounts of about 50 µg. [W. Blott et al., *J. Natl. Cancer Institute*, 85(18):1483-92 (1993); H. P. Leis, *Int. Surg.*, 76:1-5 (1991)]. Chromium is believed to play a role in modulating the symptoms of diabetes. [G. Mahdi and D. Naismith, *Ann. Nutr. Metab.*, 35:65-70 (1991)].

Nutritional supplementation of the human diet with metals, using inorganic or organometallic sources for the metals, has met with limited success. Safety and efficacy in the human metabolism of such metals has been questioned, since most inorganic forms of metals are known to have appreciable toxicity. For example, selenium is usually administered as selenium trioxide species—an agent which is extremely toxic. Trivalent chromium has been administered as inorganic chromium, typically chromium chloride or chromium acetate, or as organometallic species such as chromium picolinate or chromium nicotinate, but each of these forms of chromium has been shown to be toxic in one fashion or another, reflecting a major shortcoming in their use in nutritional supplements. In addition, inorganic forms of such metals generally have a low bioavailability, making their use in nutritional supplements questionable.

Supplementation of the human diet with metal-enriched yeast products has been sought as an alternative. Potential advantages of administering a metal derived from yeast as a nutritional supplement over non-yeast derived forms are that the toxicity of the metal will be lower in yeast-derived organometallic compounds, and that since yeast-derived organometallic compounds are more soluble, such compounds will be better metabolized by the human body. However, a drawback of using yeast-derived metallic material as a food supplement is that rather large amounts of yeast are usually needed in order to acquire the proper dosage, since the levels of metal ion produced in yeast typically range from about 500 to 2000 ppm (µg/g)—levels which would require ingestion of large amounts of yeast if the nutritional benefit of the organometallic compounds is to be realized.

DESCRIPTION OF THE PRIOR ART

Skogerson, U.S. Pat. No. 4,348,483, discloses a method for producing chromium-enriched yeast by incubating yeast

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in an aqueous solution of inorganic chromium salts, such as CrCl₃, with growth media. Although the chromium content of the yeast is about 500 to 1000 ppm, the process entails, to a large degree, internalization of chromium without metabolization of the inorganic chromium salt so that there is a high probability that a significant, if not all the chromium found in the chromium-enriched yeast is inorganic chromium. Hence, to the extent that the chromium produced in this process is merely trivalent chromium salts mixed with the structural material of yeast, the chromium produced using this method does not possess high bioactivity and is also toxic if ingested in high doses.

Szalay, U.S. Pat. No. 4,343,905, teaches a method of concentrating chromium in Brewer's yeast by cultivating the yeast in a broth where the source of trivalent chromium is from a mixture of chromium oxide and certain amino acids. Although this method yields yeast with an intracellular chromium concentration of about 2000 ppm, 80% of which is reported to as yeast-metabolized chromium, this method encounters difficulties due to the insolubility of the chromium oxide. Also, similar to U.S. Pat. No. 4,348,483, internalization without metabolization of the chromium oxide is highly probable, and will likely result in chromium oxide, known to have appreciable toxicity to the human system, remaining in its toxic form.

The isolation and selection of a particular strain of Vietnamese yeast for assimilating about 300 ppm selenium metal is known. [Dang Hong Thuy, et al., *Tap Chi Duoc Hoc*, (4):9-12 (1992)]. Assimilation of inorganic selenium by Brewer's yeast, when grown in the presence of 150 ppm selenium trioxide disodium salt, produced a yeast product having about 1000 ppm selenium, and where about 3% of this was inorganic selenium, about 30% was selenoamino acids, and the remainder was present as other yeast-derived organoselenium compounds. [Xie, L. et al., *Weishenwu Xuebao*, 30(1):36-40 (1990)].

A method for preparing yeast-derived germanium has been taught by Komatsu, Japanese Patent 77-46138770420. However, this method involves the preparation of germanium yeast using a highly toxic form of germanium, GeO₂, as the source of germanium for the feed and cultivation of the yeast. The major shortcoming of this method is it results in an appreciable content of non-metabolized GeO₂ by-product. Since GeO₂ is a highly toxic agent, this method is not useful as a dietary supplementation for the human diet.

There remains a need for novel yeast strains that metabolize metal ions to provide a non-toxic yeast product that provides a form of the metal that is highly metabolizable by the human system and that is of sufficient concentration so that the product is suitable for the commercial marketplace for nutritional supplements.

SUMMARY OF THE INVENTION

The present invention overcomes the shortcomings of the prior art by providing methods for isolating and culturing a novel yeast strain of *Saccharomyces boulardii sequela*, and for using that yeast strain as a biological source for producing forms of metal ions that are non-toxic and highly metabolizable by the human body, and which are useful for supplementation of the human diet. This discovery is based on a process for isolating and purifying the novel yeast strain comprising the steps of:

- (a) selecting an appropriate location to collect fertile samples containing the desired yeast strain;
- (b) sampling the soil to insure the desired yeast species is present;

- (c) isolating the yeast strains of the soil sample;
- (d) screening the yeast;
- (e) cultivating the yeast;
- (f) storing of the yeast; and
- (g) producing organometallic compositions using the yeast.

Hence, it is an object of the present invention to provide a method for isolating, cultivating the pure yeast strain *Saccharomyces boulardii sequela* PY31—a novel strain of *Saccharomyces boulardii sequela*.

It is another object of the present invention to provide a biosynthetic method which employs yeast strain *Saccharomyces boulardii sequela* PY31 in preparing organometallic complexes with high biological activity.

It is a further object of the present invention to provide improved forms of metal ions (included in a dried yeast product) that are derived from yeast strain *Saccharomyces boulardii sequela* and that are non-toxic and highly metabolizable by the human body.

It is still another object of the present invention to provide a method for the production of chromium-enriched yeast, where the source of chromium for metabolism by the yeast is a trivalent chromium chelate complex of niacin and glycine, and where the yeast source is *Saccharomyces boulardii sequela* PY31.

It is another object of the present invention to provide a yeast strain that will assimilate germanium metal and provide a product that is non-toxic to the human system and a form of germanium that is highly metabolizable by the human system.

It is a further object of the present invention to provide a yeast strain that will assimilate selenium metal and provide a product that is non-toxic to the human system and a form of selenium that is highly metabolizable by the human system.

It is yet a further object of the present invention to administer the dried yeast product of the present invention to humans to promote good nutritional health.

It is still another object of the present invention to provide forms of metal ions that are non-toxic to the human body and, when used as food supplements, reduce the susceptibility of the human body to chronic disorders, such as heart disease, diabetes, and possibly cancer.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the isolation and purification of a new strain of Baker's (or Brewer's) yeast, *Saccharomyces cerevisiae*, and to certain methods of cultivating this new strain of yeast that yields dried yeast mass having an enriched content of the metal ion where the form of this metal ion engenders high biological activity, and to uses of such as a nutritional supplement for the human diet. Specifically, *Saccharomyces cerevisiae* and *Saccharomyces boulardii sequela* are of the same genus, and *Saccharomyces boulardii sequela* is described as a synonym of *Saccharomyces cerevisiae*. [Barnett et al., *Yeasts: Characteristics and Identification*, Cambridge Univ. Press (1990)].

More particularly, the present invention teaches a method for isolating a novel yeast strain of *Saccharomyces boulardii sequela* from raw soil samples, and cultivating it to yield quantities of yeast at a scale sufficient for developmental research and for production of commercial products. The novel strain of yeast of the invention, *Saccharomyces boulardii sequela* PY31 has been deposited in an International Repository in accord with the Budapest Treaty and has been

assigned ATCC No. 74,366. American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Va. 20110-2209.

Specifically, the method for isolating a novel yeast strain of the present invention comprises:

- (1) identifying a location for collection of a soil sample, which is proximal to a germanium mine (i.e., within 100 yards of a germanium mine);
- (2) sampling the soil by removing about 200 g from a depth of 5 cm to 20 cm, and transporting the sample using a sterilized bag;
- (3) growing the living material on three different mediums which support the growth of all yeast, each that selectively kills bacteria without killing the yeast;
- (4) separating the yeast from other living matter and then repeating this process until yeast can be grown without bacterial contaminants;
- (5) selecting and restreaking the yeast colonies, and repeating this process three times;
- (6) selecting the yeast colonies most vital for growth in a medium enriched with germanium;
- (7) growing the selected colonies each on malt extract agar or dextrose agar, and selecting which colonies appear most robust, and;
- (8) cultivating the selected yeast by growing 1–2 slants of the yeast for about 2 days at about 30° C. and then transferring to the cultivated yeast about 100 ml. of malt extract broth and then incubating at about 30° C. for 8–10 hours, then adding to the incubated mixture about 500 mL of malt extract broth and then growing the resulting mixture at about 30° C. overnight.

The present invention also includes a process for producing an organometallic yeast product which comprises the steps of:

- (1) preparing a solution of the metal ion in warm distilled water and then filtering;
- (2) adding the live yeast culture of the isolated yeast strain *Saccharomyces boulardii sequela* PY31 and incubating as a mixture with the metallic ion with gentle shaking action for about 90 minutes;
- (3) adding yeast growth nutrients and incubating at about 30° C. for about 24 hours;
- (4) recovering and concentrating the yeast cells from the aqueous growth media;
- (5) washing the recovered yeast cells to remove extracellular unprocessed metallic species; and
- (6) pasteurizing and drying the washed yeast cells.

The present invention teaches a use of the novel yeast strain *Saccharomyces boulardii sequela* PY31 for preparing metal-enriched yeast forms. For example, the present invention has been used to prepare a germanium-enriched yeast product that has a high intracellular content of organically bound germanium in a form that is highly metabolizable by the human system and that is non-toxic to the human system. The method of this invention which comprises contacting live yeast cells in a aqueous suspension of dicarboxyethylgermaniumsesquioxide at levels between 1,000 ppm and 20,000 ppm, and preferably between 10,000 ppm and 20,000 ppm, and most preferably 20,000 ppm of the dicarboxyethylgermaniumsesquioxide, under controlled pH of about 4.2 to about 5.5, and preferably about 4.8 to about 5.3, and most preferably between about 4.9 and about 5.2, and temperature from about 20° C. to about 35° C., preferably 28° C. to 32° C. Then, the yeast and germanium mixture

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is incubated for about 5 minutes to about 120 minutes, preferably about 20 minutes to about 100 minutes, and most preferably about 90 minutes, and then growth media is added to induce growth, followed by incubating the resulting suspension with shaking at about 200 rpm for a period of at least about 10 hours, preferably from about 15 hours to about 60 hours, and most preferably about 24 hours, at a temperature of about 25° C. to about 35° C., and preferably about 30° C. The mixture is then centrifuged at about 3,500 rpm for about 10 minutes, the solid isolated and washed with the solvent to rid completely of extracellular germanium. The resultant mixture is pasteurized and dried to produce a dry yeast product.

The present invention also has been used for preparing a chromium-enriched yeast product that has a high intracellular content of organically bound trivalent chromium in a form, or forms, which are highly biologically active and non-toxic. The method for preparing the chromium-enriched yeast comprises contacting live yeast cells (*Saccharomyces boulardii sequela* PY31) in an aqueous suspension of chromium chelate complex of chromium glycinate dinitrate at levels between about 200 ppm and about 20,000 ppm chromium complex, and preferably about 500 ppm to about 15,000 ppm and most preferably about 7,500 ppm to about 10,000 ppm of the chromium complex, under controlled pH of about 4.2 to about 6.0, and preferably from about 4.5 to about 5.3, and temperature from about 2° C. to 35° C., preferably 28° C. to 32° C. The resultant mixture is incubated for about 5 minutes to about 120 minutes, preferably about 20 minutes to about 95 minutes, and most preferably about 90 minutes, and then growth media is added to induce growth, followed by incubation of the resulting suspension with shaking at about 200 rpm for a period of at least about 10 hours, preferably from about 15 hours to about 60 hours, and most preferably about 20 hours, at a temperature of about 25° C. to about 35° C., and preferably about 30° C. The resultant mixture is then centrifuged at about 3,500 rpm for about 10 minutes, the solid isolated and washed with the solvent to rid the mixture completely of extracellular chromium. The resultant mixture is then pasteurized and dried to produce a dry yeast product.

The present invention may also be used to prepare a selenium-enriched yeast product that has a high intracellular content of organic selenium in a form which is highly biologically active and substantially non-toxic. The process for obtaining the selenium-enriched yeast product is analogous to the process for obtaining the germanium and chromium-enriched yeast products and is believed to be within the ordinary skill in the art. Indeed, the above-described process may be used to assimilate other organo-metallic compounds which are known to be necessary to the human diet.

To prepare the yeast compositions of the invention for use as a dietary supplement, the yeast product is combined as the active ingredient in intimate admixture with a suitable carrier according to conventional compounding techniques. This carrier may take a wide variety of forms depending upon the form of preparation desired for administration, e.g., oral, sublingual, nasal, or parenteral.

In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. For oral liquid preparations (e.g., suspensions, elixirs, and solutions), media containing for example, water, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used. Carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to prepare oral solids (e.g., powders,

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capsules, pills, and tablets). Controlled release forms may also be used. Because of their ease in administration, tablets, pills, and capsules represent advantageous oral dosage unit forms, in which cases solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques.

For parenteral products the carrier will usually comprise sterile water, although other ingredients may be included, e.g., to aid solubility or for preservation purposes. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents, adjuvants, and the like may be employed.

A composition of the present invention is generally effective when parenterally administered in amounts ranging from about 50 µg/dose (1 dose per body weight of about 75 kg) to about 200 µg/dose of composition. This is equivalent to about 5 mg/dose to about 1 g/dose of the dried yeast germanium-containing product. When orally administered, the compositions of the present invention are generally effective in approximately the same amounts as the parenteral products. Activity at this level makes the compositions particularly well suited for formulations in tablet size for oral administration. The above dosage ranges are likely to be administered at varying periods for humans, for example, from daily administration to administration at least 5 times per week. However, ultimately, the dosage regiment will depend upon the particular needs of the user.

The following examples are illustrative only and do not limit the invention in any fashion.

EXAMPLE 1

Yeast strain *Saccharomyces boulardii sequela* PY31 was isolated and purified as follows. Soil samples were collected (about 200 g per sample) from a depth of about 5 cm to about 20 cm, at a location near a germanium mine proximal to St. George, Utah. The sampling occurred in the daytime, close to where mineral aggregates could be observed and as moist as possible, where a temperature of about 28° C. to about 30° C. and a pH of the soil between about 5.5 to about 6.0 were measured. The samples were stored in a sterilized bag at about 5° C. (ice chest). The samples were then secured within the laboratory within 1-2 days, and were processed a few hours after being so secured. About 1 g of each sample (a total of 10 samples was collected) was added to about 99 g of malt broth (pH 7.4) or lactose broth (pH 6.9 [DIFCO]), and this was shaken at 200 rpm for 1 hour.

The yeast colonies that were the fastest growing colonies were selected as follows. Serial dilutions (10 fold) were made and each dilution was streaked onto an agar plate and incubated. From these plates, a dilution that gave rise to a separate and independent colony of cells that grew well was identified. After the yeast colonies developed fully, they were carefully inspected with a microscope, and one colony of each morphological type was picked and purified by replating on to three types of agar that support yeast growth but inhibits the growth of bacteria. Specifically, several types of growth media were used: malt extract agar (pH 4.7 [DIFCO]) with 0.1% chlorophenicol or ampicillin (50 µg/L), Sabouraud dextrose agar (pH 5.6 [DIFCO]) with 0.1% chlorophenicol or ampicillin (50 µg/L), and potato dextrose agar (pH 5.6 [DIFCO]) with 0.1% chlorophenicol or ampicillin (50 µg/L). Each of these agar plates contained a substance that kills bacterial contaminants. The isolated yeast strain was streaked onto each of the three different types of agar plates.

The colonies were counted after 2-7 days of incubation at 28° C. The colonies that appeared to be the most well formed

[See, e.g., Colom'e J. S., et al., *Laboratory Exercises in Microbiology*, West Publishing Co. 68-69 (1986)] were selected and were restreaked, and this procedure was repeated at least 3 times.

The yeast strain *Saccharomyces boulardii sequela* PY31 was selected based on its superior vitality when grown in the presence of an organogermanium species (dicarboxyethylgermaniums sesquioxide) and germanium dioxide, and this was carried out as follows. A 100:1 dilution of actively growing yeast culture (isolated as per the protocol described above) was made, and about 10 mL aliquots were added to 20 mL test tubes containing 10,000 ppm dicarboxyethylgermaniums sesquioxide, and to a 20 mL test tube containing about 50 ppm of germanium dioxide, and these were each incubated at about 30° C. for 2 days. The increase in absorbance (which reflects total yeast density and, therefore, the total amount of yeast) was measured by monitoring the optical density at 590 microns (OD₅₉₀) [Beckman DU 460]. Two different types of germanium were tested for incorporation into the novel yeast strain. Specifically, germanium sesquioxide is an organic form of germanium that is not toxic to humans, while germanium dioxide is an inorganic compound and is highly toxic to humans. Although both forms of germanium were tested, since certain strains of yeast find germanium dioxide toxic, and since the low solubility of germanium dioxide limits the exposure levels for the yeast culture to germanium, the present invention uses germanium sesquioxide as the form of germanium in the culture media.

These selected yeast cultures were streaked on malt extract agar and potato dextrose agar and selected the colonies that were the most well-formed. The yeast strain *Saccharomyces boulardii sequela* PY31 was chosen as far superior in the ability to grow under the above-described conditions, from malt extract agar with ampicillin. Yeast strain *Saccharomyces boulardii sequela* is characterized by a creamy, non-mucoid, slightly raised colonies and budding cells. This yeast grows well in the presence of germanium. The yeast strain *Saccharomyces boulardii sequela* PY31 was cultivated by subjecting one to two slants of the yeast to incubation at 25° C. to about 30° C. for 2 days and transferred the resulting culture to 100 mL of malt extract broth (pH 4.7 [DIFCO]), and then this was incubated at about 30° C. for 8-10 hr, and then 500 mL of malt extract broth was added and this was incubated at 30° C. overnight. The growth of the cells was monitored by checking the OD₅₉₀ and counting the number of yeast cells under the microscope. This yeast product can be used directly for the cultivation and harvesting of metal-enriched yeast.

EXAMPLE 2

This example describes a procedure to produce a germanium-enriched yeast using the novel yeast strain of the present invention. The yeast strain *Saccharomyces boulardii sequela* PY31 was cultivated and harvested in a pure form as follows. One slant of yeast was incubated for two days at 30° C., and then grown in 200 mL of Malt extract at 30° C., shaken at 200 rpm for 8 hrs, and then to this was added 300 mL of malt extract and the resulting mixture was incubated at 30° C. overnight. A stock solution (10,000 ppm) of dicarboxyethylgermaniums sesquioxide was prepared as follows. To 300 mL of distilled water at ambient temperature was added 3.0 g of dicarboxyethylgermaniums sesquioxide [Westar Nutrition Inc.] and the resulting mixture was warmed to 40-60° C., were it was maintained for 1 hour. The pH of the cooled homogeneous solution was adjusted to 5.2 and then this was filtered through cellulose acetate membrane [Corning].

The growth medium was prepared as follows. 79° Brix molasses (670 g) [TCT, Gold Coast] was diluted to 1 L with distilled water, then 2.72 g of KCl was added, followed by 2.72 g of MgSO₄·7H₂O and then 29.28 g of NH₄H₂PO₄, and this was stirred to homogeneity. To this was added enough water to reach a final volume of 2 L (250 Brix molasses solution). The mixture was tested for sugar content by using a hydrometer, final pH is 5.0. This was subjected to autoclave at 121° C. for 15 minutes. The yeast were cultivated as follows. To 250 mL of the stock dicarboxyethylgermaniums sesquioxide solution was added 30 mL of yeast strain *Saccharomyces boulardii sequela* PY31 and the resulting suspension was shaken for 90 minutes, and then 60 mL of 25° Brix molasses solution was added and the resulting mixture was shaken at 200 rpm for 24 hours at 30° C. This mixture was centrifuged at 3,900 rpm for 10 minutes, the supernatant removed, then the yeast cells were washed once with 100 mL of 0.1M EDTA (pH = 7.8), and 0.01 M Na₂HPO₄ buffer solution, and then four times with 100 mL of distilled water. The resulting yeast cream was dried in vacuo and then the germanium content of the yeast was measured using atomic absorption techniques. To accomplish this measurement, 0.5 g of the dried yeast sample is transferred to a 50 mL volumetric flask. To the flask, 5 mL of concentrated HNO₃ is added and left overnight. The flask is then placed in a boiling water bath for four hour under a hood. After the flask is removed and has cooled, distilled water is added in sufficient amount to fill the flask to its 50 mL line. The resultant solution is then filtered through #2 Whatman filter paper into a round bottom flask. About 10 mL of the sample is then measured for its germanium content using an atomic absorption spectrometer [Beckman Instruments] set at a wavelength of 265.7 nm, a slit width of 0.2 nm, and a germanium lamp current at 35 mA. The final concentration of germanium was 5,404 ppm.

EXAMPLE 3

This example describes a procedure to produce a germanium-enriched yeast using the novel yeast strain of the present invention. The yeast strain *Saccharomyces boulardii sequela* PY31 was cultivated and harvested in a pure form as follows. One slant of yeast was incubated for two days at 30° C., and then grown in 240 mL of 2.4% potato dextrose broth at 30° C., shaken at 200 rpm for 8 hrs, and then to this was added 240 mL of 2.4% potato dextrose broth and the resulting mixture was incubated at 30° C. overnight. A stock solution (10,000 ppm) of dicarboxyethylgermaniums sesquioxide was prepared as follows. To 300 mL of distilled water at ambient temperature was added 3.0 g of dicarboxyethylgermaniums sesquioxide [Westar Nutrition Inc.] and the resulting mixture was warmed to 40-60° C., were it was maintained for 1 hour. The pH of the cooled (about 25° C.) homogeneous solution was adjusted to about 5.1 and then this was filtered through cellulose acetate membrane [Corning].

The growth medium was prepared as follows. 79° Brix molasses (670 g) [TCT, Gold Coast] was diluted to 1 L with distilled water, then 2.72 g of KCl was added, followed by 2.72 g of MgSO₄·7H₂O and then 29.28 g of NH₄H₂PO₄, and this was stirred to homogeneity. To this was added enough water to reach a final volume of 2 L. The mixture was tested for sugar content by using a hydrometer, final pH is 5.0. This was subjected to autoclave at 121° C. for 15 minutes.

The yeasts were cultivated as follows. To 250 mL of the stock dicarboxyethylgermaniums sesquioxide solution was added 250 mL of yeast strain *Saccharomyces boulardii sequela* PY31 and the resulting suspension was shaken for

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120 minutes, and then 35 mL of 20% glucose solution was added and the resulting mixture was shaken at 200 rpm for 16 hours at 30° C. This mixture was centrifuged at 3,900 rpm for 10 minutes, the supernatant removed, then the yeast cells were washed once with 100 mL of 0.1M EDTA (pH =7.8) and 0.01 M Na₂HPO₄ buffer solution, and then four times with 100 mL of distilled water. The resulting yeast cream was dried in vacuo and then the germanium content of the yeast was measured using atomic absorption techniques. To accomplish this measurement, 0.55 g of the dried yeast sample is transferred to a 50 mL volumetric flask. To the flask, 5 mL of concentrated HNO₃ is added and left overnight. The flask is then placed in a boiling water bath for four hours under a hood. After the flask is removed and has cooled, distilled water is added in sufficient amount to fill the flask to its 50 mL line. The resultant solution is then filtered through #2 Whatman filter paper into a round bottom flask. About 10 mL of the sample is then measured for its germanium content using an atomic absorption spectrometer [Beckman Instruments] set at a wavelength of 265.7 nm, a slit width of 0.2 nm, and a germanium lamp current at 35 mA. The final concentration of germanium is 1,418 ppm.

Numerous modifications and variations of the present invention are included in the above-identified specification and are expected to be obvious to one of skill in the art. It is also intended that the present invention cover modifications and variations of the compositions and method for using them to accomplish their claimed uses within the scope of the appended claims and their equivalents.

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We claim:

1. A formulation for the production of an edible yeast product comprising:

Saccharomyces boulardii sequela strain ATCC 74366 and an aqueous suspension of chromium glycinate dinicotinate; wherein the concentration of chromium glycinate dinicotinate in the aqueous suspension is sufficient to yield intracellular, organically bound chromium at a concentration of from about 500 µg to about 3000 µg per gram of dried yeast solids when the formulation is incubated for about 5 to about 120 minutes and then grown for about 15 to about 60 hours after the addition of growth media.

2. The formulation of claim 1 wherein the aqueous suspension has a concentration of chromium glycinate dinicotinate between about 200 ppm and about 20,000 ppm chromium glycinate dinicotinate.

3. The formulation of claim 2 wherein the aqueous suspension has a concentration of chromium glycinate dinicotinate between about 500 ppm and about 15,000 ppm chromium glycinate dinicotinate.

4. The formulation of claim 3 wherein the aqueous suspension has a concentration of chromium glycinate dinicotinate between about 7500 ppm and about 10,000 ppm chromium glycinate dinicotinate.

* * * * *

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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-067099- -00004-0000
Fecha: 2009-10-28 16:47:57 Dep. 2020 NUECREACIONE
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Referencia : Expediente N° 08 67099
Asunto : Oposición a la solicitud de patente de Invención titulada
"COMPOSICIONES FARMACÉUTICAS QUE
COMPRENDEN SUSTANCIAS INHIBIDORAS DE LAS
LIPASAS INTESTINALES COMBINADAS CON UN
COMPLEJO O COORDINADO DE DINICOTINATO DE
CROMO PARA SU USO EN EL TRATAMIENTO Y
CONTROL DE LA OBESIDAD O SOBREPESO"
Solicitante : WORLD-TRADE IMPORT-EXPORT, WTIE, AG
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 606 del 31 de julio de 2009

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 "COMPOSICIONES FARMACÉUTICAS QUE

COMPREDEN SUSTANCIAS INHIBIDORAS DE LAS LIPASAS INTESTINALES COMBINADAS CON UN COMPLEJO O COORDINADO DE DINICOTINATO DE CROMO PARA SU USO EN EL TRATAMIENTO Y CONTROL DE LA OBESIDAD O SOBREPESO”, cuyo titular es WORLD-TRADE IMPORT-EXPORT, WTIE, AG, 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 **DINICOTINATO**. 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 1 de julio de 2008 reivindicando prioridad bajo la solicitud MX2005PA14090 del 2005-12-20; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 605 del 30 de

junio de 2009, cuya publicación internacional corresponde a la WO2007073134 del 2007-06-28.

- 2.2. La solicitud colombiana 08 67099 objeto de la presente oposición, se refiere a una composición farmacéutica sinérgica que comprende una combinación sinérgica de un inhibidor de la lipasa intestinal y un complejo O-coordinado de dinicotinato de cromo para el tratamiento de la obesidad y el sobrepeso; donde la combinación sinérgica, en la cual el inhibidor de la lipasa intestinal es el Orlistat y/o cualquiera de sus sales y un complejo O-coordinado de dinicotinato de cromo conocido como dinicotinato de cromo y/o cualquiera de sus sales.
- 2.3. En primera instancia, se debe advertir que algunas reivindicaciones también se refieren a un método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)”*, los usos no están contemplados como patentables; y, Artículo 20.- *“No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso y a un método de tratamiento no sería patentable.
- 2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN 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 afecta la patentabilidad de la presente solicitud:

- D1: WO2004078113 publicada el 16 de septiembre de 2004.
- D2: US6159466 publicada el 12 de diciembre de 2000.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela un método para impedir o tratar la obesidad y complicaciones relacionadas con la obesidad en un sujeto que implica una monoterapia con un inhibidor COX-2 o una terapia de combinación con un inhibidor COX-2 y un agente de pérdida de peso convencional. Según esta anterioridad D1 se definen un método para prevenir o tratar la obesidad y las complicaciones relacionadas con la misma, utilizando una monoterapia con un inhibidor de la ciclooxigenasa 2 (COX-2) o una terapia combinada de un inhibidor de COX-2 con uno o más agentes reductores de peso, donde dichos agentes se seleccionan entre un inhibidor de la lipasa, en concreto orlistat o derivados de cromo, tal como el picolinato de cromo (ver reivindicaciones 2, 8 y 9). Este documento D1, por lo tanto ya revela combinaciones de orlistat con derivados de cromo tal como el picolinato de cromo para el tratamiento de la obesidad.

2.6. Por su parte, el documento D2 revela en el resumen que la invención comprende una composición acuosa para una dieta humana, con compuestos metálicos en formas biológicamente activas como un complemento. Particularmente en la descripción, particularmente a partir de la columna 5, línea 14 y siguientes, composiciones acuosas que comprende un dinicotinato de cromo, usada para preparar un producto de levadura enriquecido por cromo que tiene un alto contenido intracelular de cromo biológicamente atado trivalente en una forma, o formas, que son biológicamente activas y no tóxicas, donde el método para preparar la levadura enriquecida por cromo comprende ponerla en contacto con

células de levadura vivas (*Saccharomyces boulardii* sequela PY31) en una suspensión acuosa del complejo de dinicotinato de cromo glicinato en niveles entre aproximadamente 200 ppm y aproximadamente 20,000 complejo de cromo ppm, y preferentemente aproximadamente 500 ppm a aproximadamente 15,000 ppm. Por lo tanto esta anterioridad D2 ya revela usos del dinicotinato de cromo en preparaciones para dietas corporales en los seres humanos. Por lo tanto, este documento objeto de oposición a la luz del documento D2 carece evidentemente de ALTURA O NIVEL INVENTIVO, dado que cualquier persona versada en la materia puede llegar de manera evidente, combinando la materia revelada aquí en la anterioridad D2 con lo indicado en el documento D1, para llegar a conformar una combinación sinérgica de un inhibidor de la lipasa intestinal tal como orlistat y un complejo O-coordinado de dinicotinato de cromo para el tratamiento de la obesidad y el sobrepeso.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08 67099 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.

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

2.8.1. 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, 20 de diciembre de 2005, cualquier persona versada en la materia puede llegar de manera evidente, combinando la materia revelada aquí en la anterioridad D2

con lo indicado en el documento D1, para llegar a conformar una combinación sinérgica de un inhibidor de la lipasa intestinal tal como orlistat y un complejo O-coordinado de dinicotinato de cromo para el tratamiento de la obesidad y el sobrepeso, sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 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”*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.9. 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.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada
“COMPOSICIONES FARMACÉUTICAS QUE COMPRENDEN

SUSTANCIAS INHIBIDORAS DE LAS LIPASAS INTESTINALES COMBINADAS CON UN COMPLEJO O COORDINADO DE DINICOTINATO DE CROMO PARA SU USO EN EL TRATAMIENTO Y CONTROL DE LA OBESIDAD O SOBREPESO”, cuyo titular es WORLD-TRADE IMPORT-EXPORT, WTIE, AG, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 606 del 31 de julio de 2009.

3. PRUEBAS

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

- D1: WO2004078113 publicada el 16 de septiembre de 2004.
- D2: US6159466 publicada el 12 de diciembre de 2000.

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: WO2004078113 publicada el 16 de septiembre de 2004.
- D2: US6159466 publicada el 12 de diciembre de 2000.

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.