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Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

"SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO"
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Doctor,
JAIRO RUBIO ESCOBAR
Superintendente de Industria y Comercio
E. S. D.

Referencia : Expediente N° 00-97644
Asunto : Remisión de información a la solicitud de patente de
Invencción titulada "COMPOSICION DE
LIBERACION DUAL DE UN INHIBIDOR DE
CICLOOXIGENASA-2".
Solicitante: PHARMACIA CORPORATION.

Yo, Luis Fernando Rincón Cuellar, abogado con tarjeta profesional N° 113438 del consejo superior de la judicatura, en mi condición de apoderado 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 por orden expresa de mi representada, con el animo de colaborar con esa Entidad en la decisión que sobre la patentabilidad de la solicitud de la referencia se tomará, me permito solicitarle, muy respetuosamente, dar curso a la siguiente información relativa al arte anterior relevante para que sea tomado en cuenta en el estudio de patentabilidad de la solicitud de patente de Invencción de la referencia.

1. PETICIÓN.

Ruego al Señor Superintendente, **NEGAR**, en los términos de artículo 48 de la Decisión 486 de 2000 de la CAN, la Solicitud de Patente de Invencción

denominada **"COMPOSICION DE LIBERACION DUAL DE UN INHIBIDOR DE CICLOOXIGENASA-2"**, cuyo solicitante es **PHARMACIA CORPORATION**, con base en los siguientes hechos y fundamentos de derecho, relacionados con el incumplimiento de los requisitos fundamentales exigidos para la concesión de Patentes de Invención, según la legislación vigente.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 26 de diciembre de 2000, reivindicando prioridad bajo US 60/181,604 .10/02/2000; y, US 60/202,270 05/05/2000, publicado en Colombia en la Gaceta de la Propiedad Industrial N° 536, bajo NP 642., pág. 221.

2.2. La solicitud colombiana 00-97644 tiene como objeto una composición farmacéutica que comprende una o más unidades de dosis administrables oralmente, incluyendo cada una primera fracción de un fármaco inhibidor selectivo de ciclooxigenasa-2 de baja solubilidad en agua en una cantidad de alrededor de 10 mg a alrededor de 400mg, estando dicha primera fracción en solución en un solvente farmacéuticamente aceptable y/o presenta en partículas sólidas de liberación inmediata con un tamaño de partícula D90 menor que alrededor de 1 μ m; y una segunda fracción de dicho fármaco en una cantidad de alrededor de 10 mg a alrededor de 400mg, estando presente dicha segunda fracción en partículas sólidas con un tamaño de partícula D90 mayor de alrededor de 25 μ m y/o en partículas de liberación controlada, liberación lenta, liberación programada, liberación temporizada, liberación por pulsación, liberación sostenida o liberación extendida; en donde dicha primera y segunda fracción se hallan presentes en una relación de alrededor de 10:1 a alrededor 1:10 en la composición. Adicionalmente, reivindica un método

para tratar una condición médica o trastorno en un sujeto donde es indicado el tratamiento con un inhibidor de ciclooxigenasa-2, que comprende administrar oralmente 1 a alrededor de 4 unidades de dosis de una composición de cualquiera de las reivindicaciones 1, 17, 19 o 25 una vez al día.

2.3. Según lo expuesto, la presente solicitud pretende reivindicar un método terapéutico tal y como lo define en la cláusula 32. Según la decisión 486 de la CAN, se establece claramente en su artículo número 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 animales"*. Lo aquí reivindicado no es más que un plan de dosificación tal como un método de tratamiento. Claramente se deduce que el objeto de la presente solicitud no puede ser objeto de patente en Colombia.

2.4. Adicionalmente, el artículo 14 de 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"*. A todas luces, un plan de dosificación tal y como lo define en el capítulo reivindicatorio en su cláusula 32, no puede reproducirse a nivel industrial. Su objeto es la derivación de practicar un método terapéutico, tal como las consecuencias de su administración. La presente solicitud carece de aplicación Industrial ya que como se demostró en el apartado interior lo que se está reclamando son las características o resultados de aplicar un método de tratamiento. Estos no son aplicables industrialmente porque primero no se obtiene un resultado mediante el empleo de materias o fuerzas de la

naturaleza; y segundo no es repetible ya que usados los medios previstos no se obtiene siempre el mismo resultado. Por lo tanto el objeto de la presente invención no cumple con el requisito de la aplicación industrial.

- D1 US 5,633,272 (1997-05-27)
- D2 EP 0 863 134 A (1998-09-09)

2.5. El documento D1 afecta directamente la novedad del presente documento dado que revela con anterioridad un inhibidor de ciclooxigenasa-2. Para ello versee ejemplo 1 del D1. En el documento D1 se revela que para propósitos terapéuticos, los compuestos activos de dicho documento anterior se combinan normalmente con uno o más adyuvantes apropiados para la ruta de administración indicada. Si se administran por vía oral, los compuestos pueden mezclarse con lactosa, sacarosa, polvo de almidón, ésteres celulósicos de ácidos alcanóicos, ésteres alquílicos de celulosa, talco, ácido esteárico, estearato magnésico, óxido magnésico, sales sódica y cálcica de ácidos fosfórico y sulfúrico, goma arábiga, alginato sódico, polivinilpirrolidona y/o poli(alcohol vinílico), y a continuación formarse como tabletas o encapsularse para una administración cómoda. Según se revela en dicho documento anterior, tales cápsulas o tabletas pueden contener una formulación de liberación controlada que puede proporcionarse en una dispersión de compuesto activo en hidroxipropilmetilcelulosa. De igual forma se define que las formulaciones para administración parenteral pueden estar en la forma de soluciones o suspensiones para inyección, estériles, isotónicas, acuosas o no acuosas. Según dicho documento anterior D1, revela particularmente en la columna 41 línea 48 a columna 42 línea 4 que una formulación que incluye un inhibidor de ciclooxigenasa-2 pueden prepararse a partir de

polvos o gránulos estériles que tienen uno o más de los portadores o diluyentes para usar en las formulaciones para administración oral. Igualmente se define que los compuestos pueden disolverse en agua, polietilenglicol, propilenglicol, etanol, aceite de maíz, aceite de semillas de algodón, aceite de cacahuete, aceite de sésamo, alcohol bencílico, cloruro sódico y/o diversos tampones. Así las cosas es claro que lo reivindicado en el presente documento objeto de remisión, se define varios adyuvantes y modos de administración ampliamente conocidos en la técnica farmacéutica. De hecho, en el documento anterior en su descripción se revelan varias presentaciones farmacéuticas para la administración un inhibidor de ciclooxigenasa-2, tal como la cantidad de compuestos terapéuticamente activos que se administran y el régimen de dosificación para tratar un estado de enfermedad con los compuestos y/o las composiciones donde se define que dependen de una variedad de factores, incluyendo la edad, el peso, el sexo y el estado médico del sujeto, la gravedad de la enfermedad, la ruta y la frecuencia de administración y el compuesto particular empleado, y así pueden variar ampliamente. Según este documento D1 en la evaluación biológica, particularmente en la columna 41, líneas 32 a 47, define las composiciones farmacéuticas pueden contener ingredientes activos en el intervalo de aproximadamente 0,1 a 2000 mg, preferiblemente en el intervalo de aproximadamente 0,5 a 500 mg y lo más preferiblemente entre aproximadamente 1 y 100 mg similar a lo reivindicado en la cláusula 1 de la presente solicitud objeto de remisión. Según este texto anterior, se revela que puede ser apropiada una dosis diaria de aproximadamente 0,01 a 100 mg/kg de peso corporal, preferiblemente entre aproximadamente 0,5 y aproximadamente 20 mg/kg de peso corporal y lo más preferiblemente entre aproximadamente 0,1 y 10 mg/kg de peso corporal. La dosis diaria puede administrarse en de una a cuatro dosis al día. A todas luces, este documento anterior revela

la misma materia reivindicada en la solicitud objeto de remisión. Por lo tanto, la presente solicitud, a la luz del documento D1, carece del requisito de NOVEDAD, dado que lo que pretende se encuentra publicado antes de la radicación de la prioridad de la solicitud Colombiana.

2.6. Por su parte, el documento D2 revela un uso de un nuevo compuesto anti-inflamatorio inhibidor de ciclooxigenasa 2, como composiciones que contiene una dosis permitida de 10 a 250 mg. Este documento D2, revela la coadministración con derivados opioides según la página 3 líneas 54 a 55. En los ejemplos 2, 2a, 2b, 2c, 3, 3a, 3b, 3c del D2 se describe comprimidos para tabletas orales que contiene 5, 10, 25 y 125 mg de un agente activo en asociación con algún excipiente preferido. Según lo expuesto en dicho documento anterior D2, en combinación con el documento D1, a todas luces, cualquier persona versada en la materia, puede deducir el plan de dosificación en 1 mg a 100 mg por dosis y uno más excipientes farmacéuticamente aceptables reivindicados en la presente solicitud. Cualquier persona versada en la materia podrá deducir lo definido en las reivindicaciones de la presente solicitud objeto de remisión, especialmente a partir de lo que dicta el documento D2 en los ejemplos, combinado con la descripción del D1 en lo concerniente al inhibidor de ciclooxigenasa 2, de manera que podrá resolver el problema planteado en la presente solicitud y llegar a la misma solución propuesta. Por lo tanto, la presente solicitud, a la luz del documento D1 en combinación con el documento D2, carece del requisito de ALTURA INVENTIVA, dado que lo que pretende es derivable del arte anterior.

2.7.1. **CARECE DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la*

técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida." A la fecha de prioridad, 5 de mayo de 2000, ya era conocido, pues como se demostró, era parte del arte anterior la materia sobre la cual busca protección en el capítulo reivindicatorio con base en el documento D1.

2.7.2. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica." A la fecha de prioridad, 5 de mayo de 2000, el documento D1 en combinación con D2, es posible deducir el uso y las alternativas farmacéuticas de composiciones de liberación dual de un inhibidor de ciclooxigenasa-2.*

2.7.3. 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 lo que se está reclamando es un método de tratamiento tal como un plan matemático de dosificación y las consecuencias de seguir dicho tratamiento. Éstos NO son aplicables industrialmente porque primero no se obtiene un resultado mediante el empleo de materias o fuerzas de la naturaleza; y segundo no es repetible ya que usados los*

medios previstos no se obtiene siempre el mismo resultado. Por lo tanto el objeto de la presente invención no cumple con el requisito de la aplicación industrial.

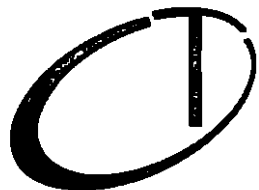
2.8. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, 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 los tres requisitos de patentabilidad.

2.9. Por consiguiente, si se concede el registro solicitado se induciría al monopolio de un producto que no cumple con los requisitos primordiales exigidos por la mencionada Decisión 486.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente remisión y negar el registro Patente de invención denominada **"COMPOSICION DE LIBERACION DUAL DE UN INHIBIDOR DE CICLOOXIGENASA-2"**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 536 del 30 de enero de 2004, en la página 221, bajo el NP 642.

3. PRUEBAS.

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



- D1 US 5,633,272 (1997-05-27)
- D2 EP 0 863 134 A (1998-09-09)

4. FUNDAMENTO DE DERECHO.

Fundamento esta remisión en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 48 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:

- D1 US 5,633,272 (1997-05-27)
- D2 EP 0 863 134 A (1998-09-09)

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 de abogado situadas en la calle 119ª N° 53-99 de esta ciudad de Bogotá.

Señor Superintendente,



C.C. 751532186



***** Pag.01
CAMARA DE COMERCIO
DE BARRANQUILLA
06*****
CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

Que por Escritura Publica Nro. 1190 del 22 de Julio de 1,976,
otorgada en la Notaria Tercera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 28 de Julio de 1,976 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 Publica Nro. 1307 del 28 de Junio de 1,979,
otorgada en la Notaria Tercera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 23 de Julio de 1,979 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 Publica Nro. 3810 del 31 de Dic/bre de 1,980,
otorgada en la Notaria Primera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 30 de Enero de 1,981 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 Publica Nro. 3755 del 10 de Nov/bre de 1,983,
otorgada en la Notaria Unica de Soledad, -----
inscrita en esta Camara de Comercio, el 22 de Nov/bre de 1,983 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 Publica Nro. 3615 del 6 de Dic/bre de 1,996,
otorgada en la Notaria 2a. de Barranquilla -----
inscrita en esta Camara de Comercio, el 20 de Dic/bre de 1,996 bajo

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

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

PROCAPS S.A. -----

el No. 67,218 del libro respectivo, la sociedad antes mencionada
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A

C E R T I F I C A

Que por Escritura Publica Nro. 3775 del 18 de Dic/bre de 1,996,
otorgada en la Notaria 2a. de Barranquilla -----
inscrita en esta Camara de Comercio, el 23 de Enero de 1,997 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	mm/dd/aaaa	Notaria	No.Ins o Reg	mm/dd/aaaa
39	1/18/1979	Notaria 3a. de Barranquilla	9,452	1/24/1979
992	4/30/1981	Notaria 1a. de Barranquilla	13,112	5/ 6/1981
1,464	8/27/1982	Notaria Unica de Soledad	15,533	9/ 8/1982
2,744	8/18/1983	Notaria Unica de Soledad	17,416	8/26/1983
3,826	7/16/1984	Notaria Unica de Soledad	19,554	7/27/1984
3,835	8/26/1985	Notaria Unica de Soledad	22,230	9/ 4/1985
2,260	9/10/1986	Notaria Unica de Soledad.	24,995	9/15/1986
1,849	7/11/1989	Notaria 2a. de Barranquilla	33,909	7/13/1989
444	2/21/1990	Notaria 2a. de Barranquilla	36,101	3/16/1990
3,090	12/17/1991	Notaria 2a. de Barranquilla	43,993	1/28/1992
269	2/ 1/1993	Notaria 2a. de Barranquilla	48,428	2/16/1993
2,342	7/28/1993	Notaria 2a. de Barranquilla	50,582	8/10/1993
3,652	11/ 9/1993	Notaria 2a. de Barranquilla	51,798	11/22/1993
3,615	12/ 6/1996	Notaria 2a. de Barranquilla	67,218	12/20/1996
89	1/16/1997	Notaria 2a. de Barranquilla	67,704	1/23/1997
2,070	7/17/1997	Notaria 2a. de Barranquilla	70,627	7/31/1997
2,281	8/ 4/1997	Notaria 2a. de Barranquilla	70,813	8/14/1997
765	4/22/1999	Notaria 3a. de Barranquilla	80,628	4/23/1999
459	2/21/2001	Notaria 2a. de Barranquilla	91,502	2/23/2001
2,608	10/ 5/2001	Notaria 2a. de Barranquilla	95,771	11/ 8/2001
1,730	7/29/2004	Notaria 2. de Barranquilla	112,999	8/26/2004

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 -----

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



***** Pag.02
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

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

PROCAPS S.A. -----

C E R T I F I C A

Direccion para notificaciones judiciales
CL 80 # 78B -201
de la ciudad de BARRANQUILLA

C E R T I F I C A

DURACION: El termino de duracion de la sociedad se fijo hasta el
18 de Agosto del ano 2,073. -----

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-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 y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados, d) 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. e)La compra, venta, exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) 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; g) Prestar los servicios de asesoria 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, cosmeticos y farmaceuticos para uso humano, animal o industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, de-

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

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

PROCAPS S.A. -----

sarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, 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 o 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 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 Accion
AUTORIZADO:		
\$*****2,000,000,000.00	2,000,000.00	1,000.00
SUSCRITO:		
\$*****1,212,449,000.00	1,212,449.00	1,000.00
PAGADO:		
\$*****1,212,449,000.00	1,212,449.00	1,000.00

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponde 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 requieran para el desarrollo del objeto social, de conformidad con

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



***** Pag.03
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A

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PROCAPS S.A. -----

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 día 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 día 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

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

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ello acreditar la ausencia del principal. La sociedad tendra un gerente general con su respectivo suplente, quienes tambien ejerceran la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el presidente y el vicepresidente. 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 superior al equivalente en pesos colombianos 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 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. Las demas funciones que les correspondan como representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El gerente lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades.-----

C E R T I F I C A

Que segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----

PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo, y por Acta No. 127 del 22 de Marzo de 2,000, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----

PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 29 de Mayo de 2,000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos: -----

J U N T A D I R E C T I V A

Principales	Suplentes
1. Minski Gontovnik Ruben	Minski Zilberblum Elliot
2. Minski Gontovnik Meyer	Minski Deitel Daniel
3. Minski Gontovnik Jose	Minski Sharon

C E R T I F I C A

Que segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----

PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
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***** C O N T I N U A *****



***** Pag.04
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A

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Presidente.	Minski Gontovnik Ruben	C.*****7,463,982=
Suplente del Presidente	Minski Minski Abraham	C.*****802,575=
Vicepresidente	Minski Gontovnik Meyer	C.*****7,461,324=
Suplente del vicepresidente	Minski Gontovnik Jose	C.*****8,671,834=

C E R T I F I C A

Que segun Acta No. 124 del 29 de Marzo de 1,999, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----

PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 4 de Agosto de 1,999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Revisor Fiscal Ppal.	Vargas Pertuz Ana Isabel	C.****32,696,645=

C E R T I F I C A

Que segun Acta No. 127 del 22 de Marzo de 2,000, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----

PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 29 de Mayo de 2,000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Suplente del Revisor Fiscal.	Lozada Villareal Milena	C.****32,748,111=

C E R T I F I C A

Que segun Acta No. 11 del 1 de Febrero de 2,001, correspondiente a la Junta Directiva en Barranquilla de la sociedad: -----

PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 12 de Febrero de 2,001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Gerente General.	Uribe Ochoa Guillermo Luis	C.****70,073,754=

C E R T I F I C A

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

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

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Que segun Acta No. 406 del 2 de Sep/bre de 2,004, correspondiente a la Junta Directiva en Barranquilla de la sociedad: -----

PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 9 de Sep/bre de 2,004 bajo el No.113,263 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Suplente del Gerente.	Tanaka Walter	C.****16,251,923=

C E R T I F I C A

Que por escritura publica No. 2.608 del 5 de Octubre del 2.001, otorgada en la Notaria 2a. de Barranquilla, inscrita en esta Camara de Comercio el 8 de Noviembre del 2.001, bajo los Nos. 95.771, 2.056, 2.057, 2.058, 2.059, 2.060, 2.061, 2.062 y 2.064 del libro respectivo, se reforma totalmente el articulo 65, contenido en la escritura publica No. 3.705 de Noviembre 6 de 1.998, de la Notaria Segunda del Circuito de Barranquilla, y se constituyen los siguientes Apoderados Generales, quienes tendran las funciones que a continuacion se indican en razon de su cargo en la sociedad: 1.-Se confiere Poder Especial, Amplio y Suficiente a los senores: WALTER TANAKA TATEKAWA, C.C. No. 16.251.923; WILLIAM ALBERTO BARROS CERRA, C.C. No. 8.715.941, para que cada uno en forma independiente en nombre y representacion de PROCAPS S.A., suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad, asi como para que responda todo tipo de requerimiento o solicitudes de informacion de las autoridades tributarias, aduaneras o cambiarias, en los ordenes Distrital, Departamental y Nacional. 2.-Se confiere Poder Especial, amplio y suficiente, a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta por la suma de US\$800.000.00 (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. GUPO A: GUILLERMO LUIS URIBE OCHO C.C. No. 70.073.754, LINO LAZALA SILVA VARGAS C.C. No. 19.260.410, JAIRO MOLINA MEJIA C.C. No. 8.706.380, CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.293. BRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, HENRY CARO DIAZ C.C. No. 19.395.298, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZ GRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requiera por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C.C. No. 33.138.497, a la Doctora MARCELA CARVAJALINO PAGANO C.C. No. 22.579.748, y al Doctor DANIEL MORENO VILLALBA, C.C. No. 19.113.210; para que cada uno representen a PROCAPS S.A., ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como: Contestar e interponer demandas y requerimientos, com-

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



***** Pag.05
C A M A R A D E C O M E R C I O
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parecer en juicios, pedir la practica de pruebas, recibir notificaciones, interponer recursos y ejercer acciones contencioso administrativas y de tutela, transigir, conciliar, recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato. Para la celebracion de cualquier acuerdo conciliatorio o transaccional, judicial o extrajudicial, cualquiera que sea su cuantia, los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la sociedad. Los Apoderados podran presentar solicitudes de devolucion y/o compensacion de impuestos y recibir los pagos por devoluciones de impuestos, firmar, notificarse y realizar todo acto necesario para cumplir con el mandato encomendado.-----

C E R T I F I C A

Que segun documento privado de fecha 7 de junio de 2000, inscrito en esta Camara de Comercio el 8 de junio de 2000, bajo el No.1.786 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a KAREN FIGUEROA GARCIA, C.C.No.32.732.070 de Barranquilla, para que en su nombre y representacion de la sociedad suscriba todas declaraciones cambiarias a que este obligada PROCAPS S.A, en el giro normal de sus negocios y operaciones sociales.--

C E R T I F I C A

Que segun Documento Privado del 13 de diciembre del 2.002, inscrito en esta Camara de Comercio el 15 de enero del 2.003 bajo el No.2.290 del libro respectivo, el señor RUBEN MINSKI GONTOVNIK, C.C.No.7.463.982, en calidad de REPRESENTANTE LEGAL, y en condicion de PRESIDENTE de PROCAPS S.A., mediante el presente documento otorgo PODER ESPECIAL al Sr. MARLON TATIS PAREDES, C.C.No.72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces. En consecuencia, el Sr. MARLON TATIS PAREDES, podra suscribir en representacion de PROCAPS S.A. declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces.-----

C E R T I F I C A

Que en esta Camara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolucion, liquidacion o nombramientos de representantes legales de la expresada sociedad.-----

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

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

PROCAPS S.A. -----

C E R T I F I C A

Que su ultima Renovacion fue el: 31 de Marzo de 2,004. -----

La informacion sobre embargos de establecimientos se suministra en
Certificados de Matricula, la de contratos sujetos a registro, en
Certificados Especiales.

C E R T I F I C A

Que los actos de registro aqui certificados quedan en firme cinco dias
habiles despues de la fecha de la publicacion en la noticia de la
correspondiente inscripcion, siempre que, dentro de dicho termino, no
sean objeto de los recursos de reposicion ante esta entidad, y/o de
apelacion para ante la Superintendencia de Industria y Comercio.--

NO CAUSA IMPUESTO DE TIMBRE


EL SECRETARIO
MARIBEL REYES OVIEDO

~~434~~ 428

ANEXO 1



US005633272A

United States Patent [19]

Talley et al.

[11] Patent Number: 5,633,272

[45] Date of Patent: May 27, 1997

[34] SUBSTITUTED ISOXAZOLES FOR THE TREATMENT OF INFLAMMATION

[76] Inventors: John J. Talley, 8772 Pine Ave., Brentwood, Mo. 63144; David L. Brown, 15504 Twingate, Chesterfield, Mo. 63017; Srinivasan Nagarajan, 16209 Forest Meadows Dr., Chesterfield, Mo. 63017; Jeffery S. Carter, 15321 Grantley Dr., Chesterfield, Mo. 63017; Richard M. Welter, 240 Hickory Ct., Lake Bluff, Ill. 60044; Michael A. Stanley, 502 Juniper Pkwy., Libertyville, Ill. 60048; Paul W. Collins, 1557 Hawthorne Pl., Deerfield, Ill. 60015; Roland S. Rogers, deceased, late of Richmond Heights, Mo. 63117, by Kathy L. Rogers, legal representative; Karen Belbert, 11930 Greenwalk Dr., St. Louis, Mo. 63146

[21] Appl. No.: 473,884

[22] Filed: Jun. 7, 1995

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 387,680, Feb. 13, 1995, abandoned.

[51] Int. Cl.⁶ C07D 261/06; C07D 261/10; C07D 261/12; C07D 261/14; A61K 31/42

[52] U.S. Cl. 514/378; 548/182; 548/186; 548/190; 548/193; 548/202; 548/203; 548/223; 548/228; 548/229; 548/232; 548/234; 548/235; 548/243; 548/245; 548/247; 548/248; 546/272.1; 544/405; 514/255; 514/340; 514/365; 514/369; 514/370; 514/374; 514/376; 514/377; 514/380

[58] Field of Search 548/247, 243, 548/245, 248; 514/380, 378

[56] References Cited

U.S. PATENT DOCUMENTS

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5,318,970 6/1994 Suzuki et al. 514/252

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Valbecoxib

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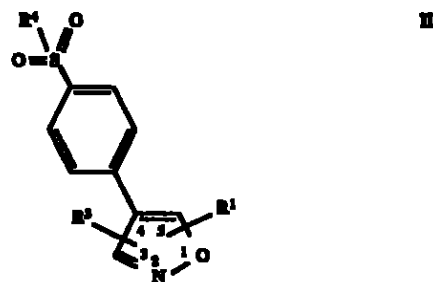
Primary Examiner—Johann Richter

Assistant Examiner—Laura L. Stockton

Attorney, Agent, or Firm—Joseph W. Bullock

[57] ABSTRACT

A class of substituted isoxazolyl compounds is described for use in treating inflammation and inflammation-related disorders. Compounds of particular interest are defined by Formula II



wherein R¹ is selected from hydroxyl, lower alkyl, carboxyl, lower carboxyalkyl, lower aminocarbonylalkyl, lower alkoxyalkyl, lower haloalkyl, lower hydroxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower arylalkoxyalkyl, lower arylthioalkyl, lower haloalkyl, lower hydroxyalkyl, cycloalkyl, cycloalkylalkyl, and aralkyl; wherein R² is selected from cycloalkyl, cycloalkenyl, aryl, and heteroaryl; wherein R³ is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkyl, lower alkoxy, lower alkoxyalkyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy, aminosulfonyl, and lower alkylthio; and wherein R⁴ is selected from lower alkyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

29 Claims, No Drawings

1

SUBSTITUTED ISOXAZOLES FOR THE TREATMENT OF INFLAMMATION

RELATED CASE

This application is a continuation-in part of U.S. patent application Ser. No. 08/387,680, filed Feb. 13, 1995 now abandoned.

FIELD OF THE INVENTION

This invention is in the field of antiinflammatory pharmaceutical agents and specifically relates to compounds, compositions and methods for treating inflammation and inflammation-associated disorders, such as arthritis.

BACKGROUND OF THE INVENTION

Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG₂, PGH₂ and PGE₂, has been a common target of antiinflammatory drug discovery. However, common non-steroidal antiinflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved.

Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase-2 (COX-2)" or "prostaglandin G/H synthase II") provides a viable target of inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects.

The references below that disclose antiinflammatory activity, show continuing efforts to find a safe and effective antiinflammatory agent. The novel isoxazoles disclosed herein are such safe and also effective antiinflammatory agents furthering such efforts. The invention's compounds are found to show usefulness in vivo as antiinflammatory agents with minimal side effects. The substituted isoxazolyl compounds disclosed herein preferably selectively inhibit cyclooxygenase-2 over cyclooxygenase-1.

Isoxazoles have been described for various uses, including the treatment of inflammation. U.S. Pat. No. DE 4,314,966, published Nov. 10, 1994, describes 3-(2-hydroxyphenyl)isoxazoles for the treatment of inflammatory disorders. WO 92/05162, published Apr. 4, 1992, describes 5-piperazinyl-3,4-diaryl-isoxazoles as having medicinal use.

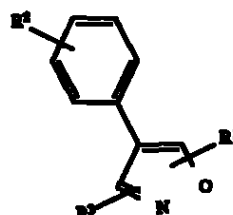
WO 92/19604, published Nov. 12, 1992, describes 5-alkene-3,4-diaryl-isoxazoles as having cyclooxygenase inhibition activity. EP 26928, published Apr. 15, 1981, describes 3,4-diaryl-isoxazole-5-acetic acids as having anti-inflammatory activity. WO 95/00501, published Jan. 5, 1995, generically describes 3,4-diaryl-isoxazoles as cyclooxygenase inhibitors.

The invention's isoxazolyl compounds are found to show usefulness in vivo as antiinflammatory agents with minimal side effects.

2

DESCRIPTION OF THE INVENTION

A class of substituted isoxazolyl compounds useful in treating inflammation-related disorders is defined by Formula I:



wherein R¹ is selected from hydroxyl, amino, alkyl, carboxyalkyl, alkoxyalkyl, aminocarbonyl, aminocarbonylalkyl, alkoxyalkyl, carboxyl, alkoxy, haloalkoxy, aralkoxy, heteroaralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, heteroaralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, aryloxyalkyl, arylthioalkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocyclo, heterocycloalkyl, aryl, alkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, heteroaralkylamino, N-alkyl-N-heteroaralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonylthio, alkylaminocarbonylthioalkyl, arylcarbonyloxyalkyl, alkoxyalkoxyalkyl, alkylaminocarbonyloxyalkyl, alkoxyalkoxythioalkyl, and alkylaminocarbonylthioalkyl;

wherein R² is one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxyalkyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, aminoalkyl, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfonyl, halo, hydroxysulfonyl, alkylsulfonyl, aminosulfonyl, haloalkylsulfonyl, alkoxy and alkylthio;

wherein R³ is selected from cycloalkyl, cycloalkenyl, aryl and heterocyclo; wherein R³ is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxyalkyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, aminoalkyl, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfonyl, aminosulfonyl, halo, alkoxy and alkylthio;

or a pharmaceutically-acceptable salt thereof.

Compounds of Formula I would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of Formula I would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such compounds of Formula I would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin related conditions such as psoriasis, eczema, burns and dermatitis. Compounds of Formula I also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention of colorectal cancer. Compounds of Formula I would be useful in treating inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, scleroderma, rheumatic fever, type I diabetes, myasthenia gravis, sarcoidosis, nephrotic syndrome, Behcet's syndrome,

polymyositis, glaucoma, hypersensitivity, conjunctivitis, swelling occurring after injury, myocardial ischemia, and the like. The compounds are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. Besides being useful for human treatment, these compounds are also useful for treatment of mammals, including horses, dogs, cats, rats, mice, sheep, pigs, etc.

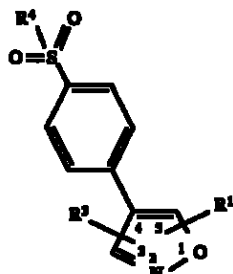
The present compounds may also be used in co-therapies, partially or completely, in place of other conventional antiinflammatories, such as together with steroids, NSAIDs, 5-lipoxygenase inhibitors, LTB₄ antagonists and LTA₄ hydrolase inhibitors.

Suitable LTB₄ inhibitors include, among others, ebisen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, Terumo compound TMK-688, Lilly compounds LY-213024, 264086 and 292728, ONO compound ONO-LB457, Searle compound SC-53228, calcitrol, Lilly compounds LY-210073, LY223982, LY233469, and LY255283, ONO compound ONO-LB-448, Searle compounds SC-41930, SC-50605 and SC-51146, and SKF compound SKF-104493. Preferably, the LTB₄ inhibitors are selected from ebisen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, and Terumo compound TMK-688.

Suitable 5-LO inhibitors include, among others, masoprocol, tenidap, zileuton, pranlukast, tepoxalin, fluprofen, fluprofen hydrochloride, enalapril phosphate, and bunaprost.

The present invention preferably includes compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2 IC₅₀ of less than about 0.5 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-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 NSAID-induced side effects.

Within Formula I there is a subclass of compounds of high interest represented by Formula II:



wherein R¹ is selected from alkyl, carboxyalkyl, alkoxyalkyl, aminocarbonyl, aminocarbonylalkyl, alkoxyalkyl, carboxyl, alkoxy, haloalkoxy, aralkoxy, heteroaralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, heteroaralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, aralkoxyalkyl, aralkylthioalkyl, hydroxyl, amino, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocyclo, heterocycloalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, heteroaralkylamino,

N-alkyl-N-heteroaralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxyalkoxyalkyl, alkylaminoalkoxyalkyl, alkoxyalkylthioalkyl, and alkylaminoalkylthioalkyl;

wherein R² is selected from cycloalkyl, cycloalkenyl, aryl and heterocyclo; wherein R³ is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxyalkoxy, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfonyl, alkylsulfonate, aminoalkoxy, halo, alkoxy and alkylthio; and

wherein R⁴ is selected from alkyl, hydroxyl, and amino; or a pharmaceutically-acceptable salt thereof.

A preferred class of compounds consists of those compounds of Formula II wherein R¹ is selected from hydroxyl, amino, lower alkyl, lower carboxyalkyl, lower alkoxyalkoxy, lower aminocarbonyl, lower aminocarbonylalkyl, lower alkoxyalkoxy, lower aralkoxy, lower heteroaralkoxy, lower cycloalkylalkoxy, lower alkylthio, lower aralkylthio, lower heteroaralkylthio, lower cycloalkylalkylthio, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower aralkoxyalkyl, lower aralkylthioalkyl, lower hydroxyalkyl, lower haloalkyl, lower cycloalkyl, lower cycloalkylalkyl, 5- or 6-membered heterocyclo, lower heterocycloalkyl, lower aralkyl, halo, lower alkylamino, lower aralkylamino, lower N-alkyl-N-aralkylamino, lower heteroaralkylamino, lower N-alkyl-N-heteroaralkylamino, lower arylcarbonyloxyalkyl, lower alkoxyalkoxyalkyl, lower aminocarbonylalkyl, lower aminocarbonylalkylthio, and lower alkylaminoalkylthio;

wherein R² is selected from cycloalkyl, cycloalkenyl, aryl, and heterocyclo; wherein R³ is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfonyl, lower alkyl, cyano, carboxyl, lower alkoxyalkoxy, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower aralkylamino, lower aminoalkyl, nitro, halo, lower alkoxy, lower alkylsulfonate, aminoalkoxy, and lower alkylthio; and wherein R⁴ is selected from lower alkyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

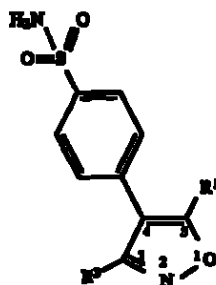
A more preferred class of compounds consists of those compounds of Formula II wherein R¹ is selected from hydroxyl, lower alkyl, carboxyl, lower carboxyalkyl, lower aminocarbonylalkyl, lower alkoxyalkoxyalkyl, lower aralkyl, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower aralkoxyalkyl, lower aralkylthioalkyl, lower haloalkyl, lower hydroxyalkyl, cycloalkyl, cycloalkylalkyl, and aralkyl; wherein R² is selected from cycloalkyl, cycloalkenyl, aryl, and heterocyclo; wherein R³ is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfonate, lower alkyl, cyano, carboxyl, lower alkoxyalkoxy, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower aralkylamino, lower aminoalkyl, nitro, halo, lower alkoxy, aminoalkoxy, and lower alkylthio; and wherein R⁴ is selected from lower alkyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula II wherein R¹ is selected from

5

hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, carboxyl, carboxypropyl, carboxymethyl, carboxyethyl, benzyl, phenethyl, aminocarbonylmethyl, methoxycarbonylmethyl, methoxycarbonylethyl, methoxymethyl, benzoxymethyl, phenylethoxymethyl, methylthiomethyl, benzylthiomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, phenyloxymethyl, phenylthiomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxymethyl, hydroxylpropyl, hydroxylethyl, cyclohexyl, cyclobutyl, cyclopentyl, cycloheptyl, cyclohexylmethyl, cyclohexylethyl, cyclobutylethyl, cyclopentylmethyl, cycloheptylpropyl, and lower aralkyl selected from benzyl and phenylethyl, wherein the phenyl ring is optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, methyl, and methoxy; wherein R^2 is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, 1-cyclopentenyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl and pyrazinyl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfinyl, ethylsulfinyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, aminosulfonyl, methylthio, ethylthio, butylthio, and hexylthio; and wherein R^4 is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

Within Formula I there is a subclass of compounds of high interest represented by Formula III:



wherein R^1 is selected from hydroxyl, alkyl, carboxyalkyl, aminocarbonylalkyl, alkoxyalkyl, carboxyl, alkoxy, haloalkoxy, aralkoxy, heteroaralkoxy, cycloalkylalkoxy, alkylthio, heteroaralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, arylalkoxyalkyl, arylthioalkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, heterocyclo, heterocycloalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, heteroaralkylamino, N-alkyl-N-heteroaralkylamino, alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxyalkoxyalkyl, alkylaminocarbonyloxyalkyl, alkoxyalkoxyalkyl, and alkylaminocarbonylthioalkyl; and

6

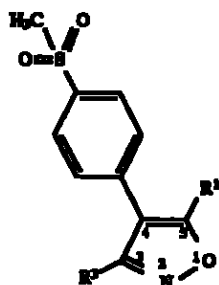
wherein R^2 is selected from cycloalkyl, cycloalkenyl, aryl and heterocyclo; wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfinyl, aminosulfonyl, halo, alkoxy and alkylthio; or a pharmaceutically-acceptable salt thereof.

A preferred class of compounds consists of those compounds of Formula III wherein R^1 is selected from hydroxyl, lower alkyl, carboxyl, lower carboxyalkyl, lower aminocarbonylalkyl, lower alkoxyalkyl, lower aralkyl, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower arylalkoxyalkyl, lower arylthioalkyl, lower haloalkyl, lower hydroxyalkyl, lower cycloalkyl, lower cycloalkylalkyl, and aralkyl; wherein R^2 is selected from cycloalkyl, cycloalkenyl, aryl, and heterocyclo; and wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfinyl, aminosulfonyl, lower alkyl, cyano, carboxyl, lower alkoxyalkyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy and lower alkylthio; or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest consists of those compounds of Formula III wherein R^1 is selected from hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, carboxyl, carboxypropyl, carboxymethyl, carboxyethyl, benzyl, phenethyl, aminocarbonylmethyl, methoxycarbonylmethyl, methoxycarbonylethyl, methoxymethyl, benzoxymethyl, phenylethoxymethyl, methylthiomethyl, benzylthiomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, phenyloxymethyl, phenylthiomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, methylthio, ethylthio, butylthio, and hexylthio; and wherein R^2 is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, 1-cyclopentenyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl and pyrazinyl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfinyl, ethylsulfinyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, aminosulfonyl, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, methylthio, aminosulfonyl, ethylthio, butylthio, and hexylthio; or a pharmaceutically-acceptable salt thereof.

A class of compounds of more particular interest consists of those compounds of Formula III wherein R^1 is selected from methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, hydroxymethyl, hydroxypropyl, methoxymethyl, difluoromethyl, trifluoromethyl, chloromethyl, cyclohexyl, cyclohexylmethyl, 4-chlorobenzyl, 3-chlorobenzyl, 4-methylbenzyl, 4-methoxybenzyl, carboxyl, carboxypropyl, carboxymethyl, carboxyethyl, methoxycarbonylmethyl, and ethoxycarbonyl; wherein R^2 is phenyl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfonyl, ethylsulfonyl, aminosulfonyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, aminomethyl, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentyloxy, hexyloxy, methylsulfonyl, methylthio, ethylthio, butylthio, and hexylthio; or a pharmaceutically-acceptable salt thereof.

Within Formula I there is a subclass of compounds of high interest represented by Formula IV:



wherein R^1 is selected from alkyl and carboxyalkyl; and wherein R^2 is selected from cycloalkyl, cycloalkenyl, aryl and heterocyclo; wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxycarbonyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminomethyl, nitro, alkoxyalkyl, alkylsulfonyl, aminosulfonyl, halo, alkoxy and alkylthio; or a pharmaceutically-acceptable salt thereof.

A family of specific compounds of particular interest within Formula I consists of compounds and pharmaceutically-acceptable salts thereof as follows:

[3-(3-fluoro-4-methoxyphenyl)-4-phenyl-isoxazol-5-yl] propanoic acid;
[3,4-diphenylisoxazol-5-yl]propanoic acid;
3-(3-fluoro-4-methoxyphenyl)-5-methyl-4-phenylisoxazole;
5-methyl-4-[4-(methylthio)phenyl]-3-phenylisoxazole;
3-(3-fluoro-4-methoxyphenyl)-5-methyl-4-[4-(methylthio)phenyl]isoxazole;
3-(3-chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylthio)phenyl]isoxazole;
[4-[4-(methylthio)phenyl]-3-phenylisoxazol-5-yl]acetic acid;
[3,4-diphenylisoxazol-5-yl]acetic acid;
[3-(3-fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid;

[3-(3-chloro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid;
5-methyl-4-[4-(methylsulfonyl)phenyl]-3-phenylisoxazole;
3-(3-chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
3-(3-chloro-4-methoxyphenyl)-5-ethyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
3-(3-fluoro-4-methoxyphenyl)-5-ethyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
3-(3,4-dichlorophenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
3-(3,4-difluorophenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
3-(3,5-difluoro-4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
3-(4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
3-(4-chlorophenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
3-(4-fluorophenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
3-(4-methylphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
4-[5-ethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-isopropyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-butyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-isobutyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-cyclohexyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-neopentyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-cyclohexylmethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-(3-trifluoromethyl-3-phenylisoxazol-4-yl)]benzenesulfonamide;
4-[5-(5-difluoromethyl-3-phenylisoxazol-4-yl)]benzenesulfonamide;
4-[5-(5-chloromethyl-3-phenylisoxazol-4-yl)]benzenesulfonamide;
4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;
4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;
4-[5-methoxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-(3-hydroxypropyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[3-(4-chlorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
4-[3-(4-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
4-[3-(3-fluoro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
4-[3-(3-aminosulfonyl-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
4-[3-(3-chloro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
4-[5-methyl-3-(3-pyridyl)isoxazol-4-yl]benzenesulfonamide;
4-[5-methyl-3-(4-pyridyl)-isoxazol-4-yl]benzenesulfonamide;
4-[3-(3-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]carboxylic acid;
4-[5-hydroxy-3-phenyl-4-isoxazolyl]benzenesulfonamide;

10

4-[5-ethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-isopropyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-butyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-isobutyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-cyclohexyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-neopentyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-cyclohexylmethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-(4-chlorophenyl)methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-trifluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-chloromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;
4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;
4-[5-methoxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[5-(3-hydroxypropyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;
4-[3-(4-chlorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
4-[3-(4-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
4-[3-(3-fluoro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
4-[3-(3-aminosulfonyl-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
4-[3-(3-chloro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
4-[5-methyl-3-(3-pyridyl)isoxazol-4-yl]benzenesulfonamide;
4-[5-methyl-3-(4-pyridyl)-isoxazol-4-yl]benzenesulfonamide;
4-[3-(3-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
[4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]carboxylic acid;
4-[5-hydroxy-3-phenyl-isoxazolyl]benzenesulfonamide;
4-[3-methyl-5-phenyl-isoxazol-4-yl]benzenesulfonamide;
4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;
4-[3-(3-fluoro-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
[3-(3-chloro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid;
5-methyl-4-[4-(methylsulfonyl)phenyl]-3-phenyl-isoxazole;
3-(3-chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
[4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]acetic acid;
[4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoic acid;
ethyl 4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoate;
[4-[4-(aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic acid; and
[3-(3-fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid.

The term "hydrido" denotes 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. Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" 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 six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like. The term "cycloalkyl" embraces saturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine. 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 either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The terms "hydroxyalkyl" and "hydroxyalkyl" embrace 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. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. 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" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "cycloalkoxy" embraces radicals having cycloalkyl radicals, as defined above, attached to an alkoxy radical. 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, tetrahydronaphthyl, indane and biphenyl. The terms "heterocyclic" and "heterocyclo" embrace saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen.

Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms (e.g. pyrrolidyl, imidazolidinyl, piperidino, piperidinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolidinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclic group containing 1 to 3 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3-to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. 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. Said "heterocyclic group" may have 1 to 3 substituents such as lower alkyl, hydroxy, oxo, amino and lower alkylamino. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio. The term "alkylthioalkyl" embraces radicals containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkyl radicals include methylthiomethyl. The term "cycloalkylalkylthio" embraces radicals having cycloalkyl radicals, as defined above, attached to an alkylthio radical. More preferred cycloalkylthio radicals are "lower cycloalkylalkylthio" radicals having cycloalkyl radicals of three to six carbon atoms. The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent $-\text{S}(=\text{O})-$ radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having alkyl

radicals of one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl. 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. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals. The terms "sulfonyl", "aminosulfonyl" and "sulfonamido" denote $\text{NH}_2\text{O}_2\text{S}-$. The term "acyl" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aryl radicals. The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-\text{CO}_2\text{H}$. The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes $-(\text{C}=\text{O})-$. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Examples of such "alkoxycarbonyl" ester radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The term "alkoxycarbonylalkyl" means a radical containing an alkoxycarbonyl radical, as defined above, attached to an alkyl radical. Examples of such "alkoxycarbonylalkyl" ester radicals include substituted or unsubstituted methoxycarbonylmethyl, butoxycarbonylmethyl and hexyloxycarbonylethyl. The terms "alkylcarbonyl", "arylcabonyl" and "aralkylcarbonyl" include radicals having alkyl, aryl and aralkyl radicals, as defined above, attached via an oxygen atom to a carbonyl radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, phenylcarbonyl and benzylcarbonyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable. The term "heterocycloalkyl" embraces heterocyclo-substituted alkyl radicals, such as pyrrolidinylmethyl, piperazinylmethyl, piperidinylmethyl, furanylmethyl, tetrahydrofurylethyl and heteroaralkyl radicals. The term "heteroaralkyl" embraces heteroaryl-substituted alkyl radicals, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolyethylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The term "cycloalkylalkyl" embraces cycloalkyl-substituted alkyl radicals such as cyclohexylmethyl, cyclopentylethyl, cyclooctylmethyl, cyclohexylethyl, and cyclobutylpropyl. The term "aralkoxy" embraces aralkyl radicals attached through an oxygen atom to other radicals. The term "aralkoxyalkyl" embraces aralkoxy radicals attached through an oxygen atom to an alkyl radical. The term "aralkylthio" embraces aralkyl radicals attached to a sulfur atom. The term "aralkylthioalkyl" embraces aralkylthio radicals attached through a sulfur atom to an alkyl radical. The term "heteroaralkoxy" embraces heteroaralkyl radicals attached through an oxygen atom to other radicals. The term "heteroaralkylthio" embraces heteroaralkyl radicals attached through a sulfur atom to other radicals. The term "aminoalkyl" embraces alkyl radicals

substituted with amino radicals. The term "alkylamino" denotes amino groups which have been substituted with one or two alkyl radicals. Suitable "alkylamino" may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "cycloalkylamino" denotes amino groups which have been substituted with one or two cycloalkyl radicals, as defined above. The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term "aralkylamino" embraces aralkyl radicals attached through an nitrogen atom to other radicals. The term "heteroaralkylamino" embraces heteroaralkyl radicals, as defined above, attached through an nitrogen atom to other radicals. The term "aminocarbonyl" denotes an amide group of the formula $-\text{C}(=\text{O})\text{NH}_2$. The term "alkylcarbonylaminomethyl" embraces radicals having one or more alkyl radicals attached to a carbonyl radical further attached to an aminoalkyl radical. The term "alkylaminomethyl" embraces radicals having one or more alkyl radicals attached to an aminoalkyl radical. The term "aryloxymethyl" embraces radicals having an aryl radicals attached to an alkyl radical through a divalent oxygen atom. The term "arylothioalkyl" embraces radicals having an aryl radicals attached to an alkyl radical through a divalent sulfur atom.

The present invention comprises a pharmaceutical composition comprising a therapeutically-effective amount of a compound of Formulas I-IV in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a method of treating inflammation or inflammation-associated disorders in a subject, the method comprising administering to the subject having such inflammation or disorder a therapeutically-effective amount of a compound of Formulas I-IV.

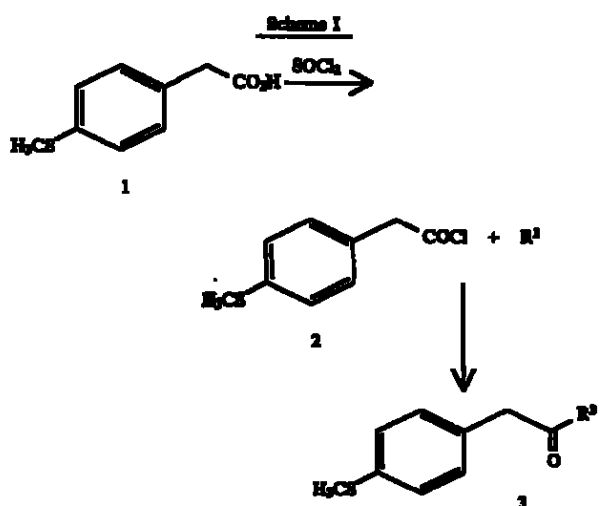
Also included in the family of compounds of Formulas I-IV are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formulas I-IV may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamolic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, alginic, β -hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formulas I-IV include metallic salts made from aluminium, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formulas I-IV by reacting, for example, the appropriate acid or base with the compound of Formulas I-IV.

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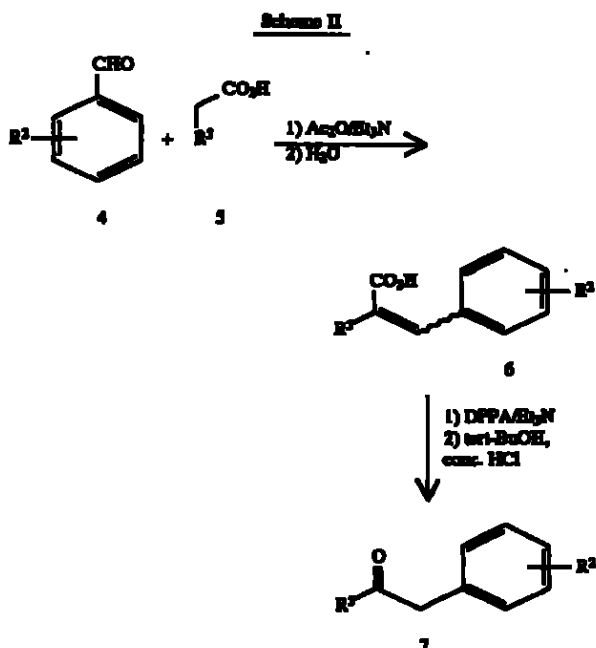
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GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be synthesized according to the following procedures of Schemes I-XIII, wherein the R^1 - R^4 substituents are as defined for Formulas I-IV, above, except where further noted.



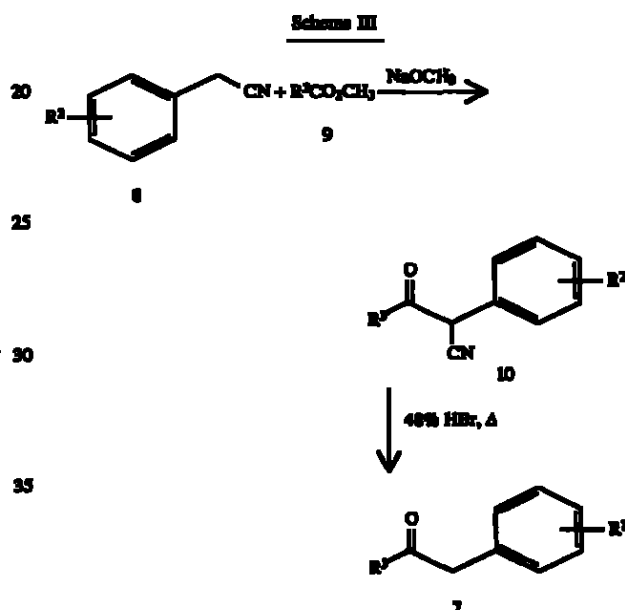
Scheme I illustrates the two step procedure used to prepare substituted desoxybenzoin derivatives 3. In step one, 4-methylthiophenylacetic acid 1 is converted to the corresponding acid chloride 2 with thionyl chloride. A variety of aromatic compounds are then acylated with 2 in the presence of a Lewis acid such as aluminum chloride to provide the desired desoxybenzoins 3 in high yield. This Friedel Crafts acylation can be performed in an inert solvent, such as dichloromethane, chloroform, nitrobenzene, 1,2-dichloroethane, 1,2-dichlorobenzene and similar solvents.



Synthetic Scheme II shows the four step procedure which can be used to prepare substituted ketone compounds 7 from

16

aldehyde 4 and acid 5. In step one, aldehyde 4 and substituted acetic acid 5 are heated together in acetic anhydride and triethylamine to form the 2,3-disubstituted acrylic acids 6 via a Perkin condensation. In step two, the addition of water produces the acids 6 free from any mixed acetoacrylic anhydrides. In step three, the acrylic acids 6 are reacted with diphenylphosphoryl azide (DPPA) and triethylamine in toluene at about 0° C. and then at room temperature to form acylazides. In step four, the crude acylazides are heated to form a vinyl isocyanate via a Curtius rearrangement. The vinyl isocyanates are trapped with tert-butyl alcohol to produce N-tert-butoxycarbonyl enamine derivatives. Acidic hydrolysis using concentrated HCl provides the substituted ketone 7 intermediates.



Synthetic Scheme III illustrates an alternative approach which can be used to prepare substituted ketone intermediates 7 via the Claisen reaction of a substituted phenylacetonitrile 8 and an acid ester 9. In the first step, a mixture of substituted phenylacetonitrile 8 and acid ester 9 are treated with a base such as sodium methoxide in a protic solvent like methanol to provide the cyanoketone 10. In step two, the cyanoketone 10 is hydrolyzed in aqueous acid such as concentrated HBr to effect hydrolysis of the nitrile and decarboxylation of the incipient carboxylic acid to produce the substituted ketone intermediates 7.

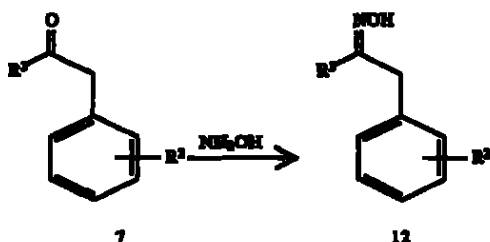
Other synthetic approaches are possible to form the desired ketones 7. These alternatives include reacting the appropriate Grignard or lithium reagents with Weinreb amides of substituted acids or acetic acids. The Weinreb methodology has been reported in *Tetrahedron Letters*, 4171 (1977).

26

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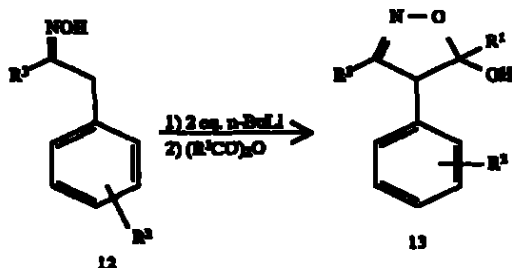
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Scheme IV



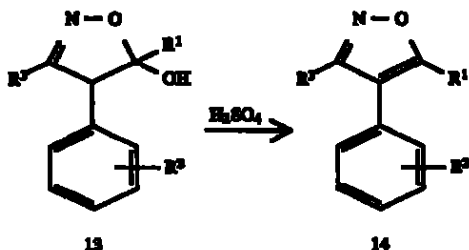
Synthetic Scheme IV shows the procedure which can be used for the preparation of oxime intermediates 12. Treatment of ketone intermediates 7 with hydroxylamine, generally prepared from hydroxylamine hydrochloride by potassium hydroxide, provides the oxime intermediates 12. A wide variety of solvents can be used for this reaction including ethanol, toluene and tetrahydrofuran.

Scheme V



Synthetic Scheme V shows the procedure which can be used for the preparation of hydrated isoxazole derivatives 13. The substituted oximes 12 are treated with two equivalents of a base such as $n\text{-butyllithium}$ in hexanes to produce a dianion which is subsequently acylated. Suitable acylating agents are anhydrides, acyl imidazoles, esters and the like. Upon quenching the reaction mixture with dilute aqueous acid, hydrated isoxazole derivatives 13 can be isolated by crystallization or chromatography.

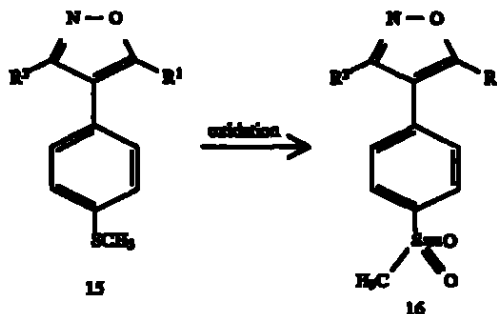
Scheme VI



Synthetic Scheme VI shows the procedure which can be used for the preparation of isoxazole analogs 14 by dehydration of the hydrated isoxazole derivatives 13. Substituted hydrated isoxazoles 13 are dissolved in an appropriate solvent such as toluene and then treated with a catalytic to stoichiometric amount of concentrated sulfuric acid to effect

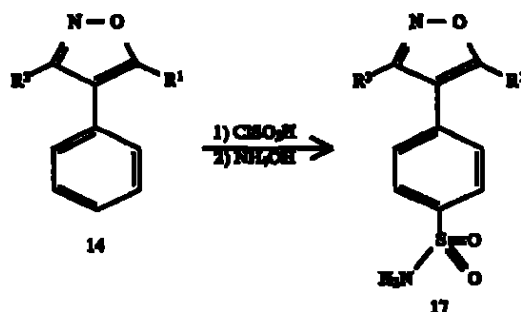
dehydration and thereby produce isoxazole derivatives 14. Other acids can also be employed to effect this transformation such as concentrated HCl , concentrated HBr and many others.

Scheme VII



Synthetic Scheme VII shows the procedure which can be used for the preparation of substituted 4-[4-(methylsulfonyl)phenyl]isoxazole analogs 16 from the corresponding 4-[4-(methylthio)phenyl]isoxazoles 15. The oxidation of an aromatic methylthio derivative 15 to the corresponding aromatic methylsulfonyl compound 16 can be accomplished in a variety of ways such as with two equivalents of meta-chloroperoxybenzoic acid (MCPBA), two equivalents of Oxone® (potassium peroxymonosulfate) and many other oxidizing agents.

Scheme VIII

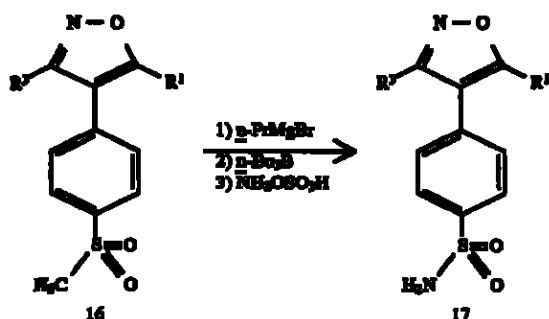


Synthetic Scheme VIII shows the procedure which can be used for the preparation of substituted 4-(4-aminosulfonyl)phenylisoxazole analogs 17 from the corresponding 4-phenylisoxazoles 14. The procedure is a two step process for the direct introduction of the sulfonamide moiety into 4-phenylisoxazoles 14 or hydrated isoxazoles 13. In step one, isoxazole 14 or hydrated isoxazole 13 is treated at about 0°C . with two or three equivalents of chlorosulfonic acid to form the corresponding sulfonyl chloride. In step two, the sulfonyl chloride thus formed is treated with concentrated ammonia to provide the sulfonamide derivative 17.

44/439

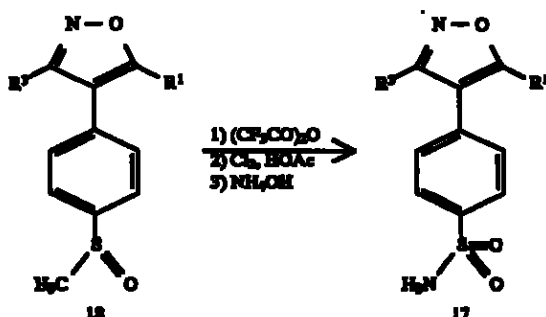
19

Scheme IX



Synthetic Scheme IX shows the three step procedure used to prepare sulfonamide antiinflammatory agents 17 from their corresponding methyl sulfones 16. In step one, a tetrahydrofuran solution (THF) of the methyl sulfones 16 are treated with an alkylolithium or alkylmagnesium (Grignard) reagent at -78°C , such as n -propyl magnesium bromide. In step two, the anion generated in step one is treated with an organoborane, such as tri- n -butylborane at -78°C , then warmed to room temperature and then heated to reflux. In step three, an aqueous solution of hydroxylamine- o -sulfonic acid is added to provide the corresponding sulfonamide antiinflammatory agents 17. This procedure is essentially that of Huang et. al., *Tetrahedron Letters*, 35, 7204 (1994).

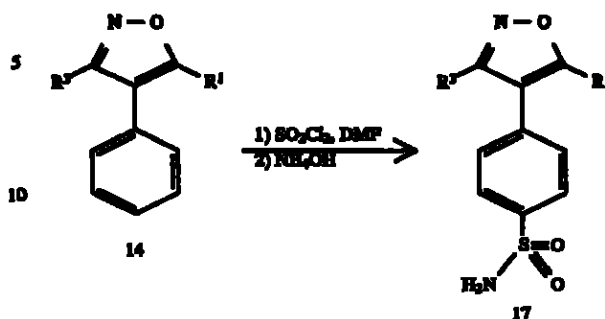
Scheme X



Synthetic Scheme X shows the three step procedure used to prepare sulfonamide antiinflammatory agents 17 from their corresponding methylsulfinyl analogs 18. Methylsulfinyl derivatives 18 are available from the corresponding methylthio compounds 15 by oxidation with one equivalent of an oxidizing agent such as MCPBA. In step one, the methylsulfinyl compounds 18 are treated with trifluoroacetic anhydride to effect Pummerer rearrangement. In step two, the crude Pummerer rearrangement product dissolved in acetic acid is treated with chlorine gas to produce a sulfonyl chloride. In step three, the sulfonyl chloride is converted to the corresponding sulfonamide antiinflammatory agents 17 by treatment with concentrated ammonia. This procedure was adapted from Kharasch, *J. Am. Chem. Soc.*, 73, 3240 (1951).

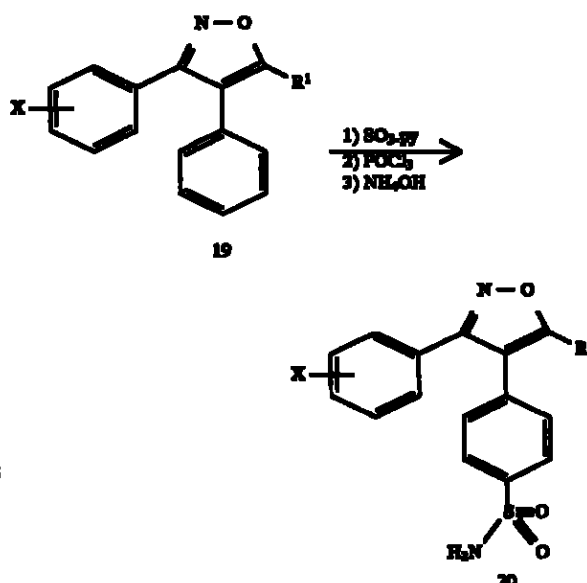
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Scheme XI



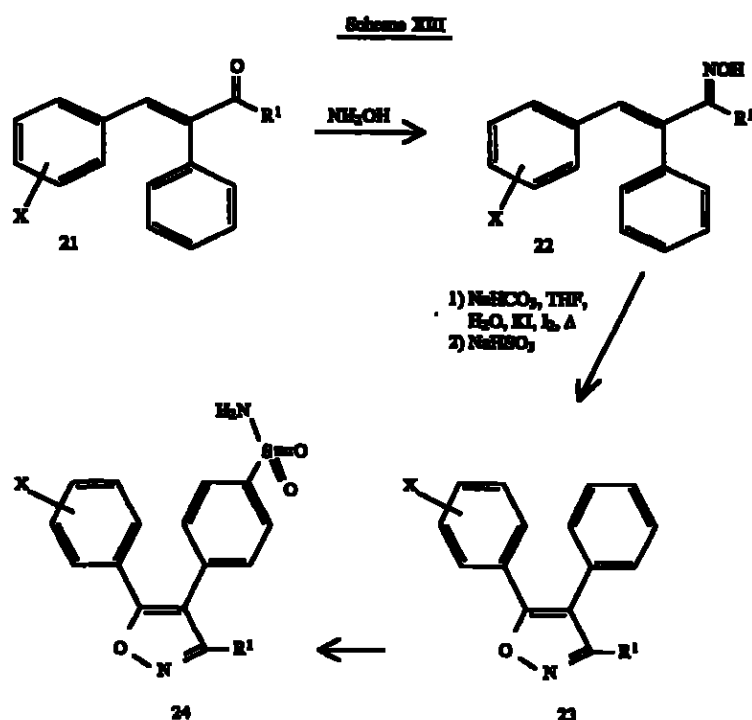
Synthetic Scheme XI shows the two step procedure used to prepare sulfonamide antiinflammatory agents 17 from their corresponding 4-phenyl isoxazole derivatives 14. In step one a mixture of sulfuryl chloride and dimethylformamide (DMF) are allowed to react at room temperature and then mixed with 4-phenylisoxazoles 14 and heated to about 100°C . The sulfonyl chloride thus formed is then treated with an excess of concentrated ammonia to provide the antiinflammatory sulfonamides 17.

Scheme XII



Synthetic Scheme XII shows the three step procedure used to prepare sulfonamide antiinflammatory agents 20 from 4-phenyl isoxazoles 19. In step one, the 4-phenylisoxazoles 19 are converted into the corresponding sulfonic acid by treatment with sulfur trioxide pyridine (pyridine) complex at about 100°C . In step two, the sulfonic acid is converted into the sulfonyl chloride by the action of phosphorus oxychloride and in step three the sulfonyl chloride is treated with excess concentrated ammonia to provide the antiinflammatory sulfonamides 20.

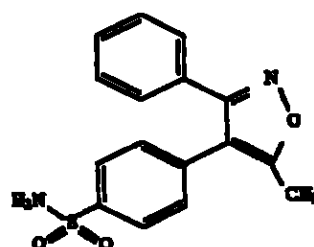
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Synthetic Scheme XIII shows the three step procedure used to prepare 4,5-diphenylisoxazole antiinflammatory agents 24 from 1,2-diphenylbutenones 21. In step one, the 1,2-diphenylketones 21 are converted to the corresponding oximes 22 by treatment with hydroxylamine in a manner similar to that shown in Scheme IV. In step two, the oxime 22 is converted to the 4,5-diphenylisoxazole 23 in two steps. The oxime 22 is reacted with potassium iodide and iodine in the presence of base, such as sodium bicarbonate and heated to form the halo intermediate. Sodium bisulfite is added to form the isoxazole 23. The isoxazole 23 is converted to the sulfonamide by any of the procedures shown in Schemes VIII, XI or XII.

The following examples contain detailed descriptions of the methods of preparation of compounds of Formulas I-IV. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated. All compounds showed NMR spectra consistent with their assigned structures.

EXAMPLE 1



4-[5-Methyl-3-phenylisoxazol-4-yl] benzenesulfonamide

Step 1. Preparation of desoxybenzoin keto-oxime.

Desoxybenzoin (20.0 g, 0.102 mol) was dissolved in toluene (200 mL). In a separate 500 mL round-bottom flask equipped with a magnetic stirring bar, hydroxylamine hydrochloride (9.21 g, 0.132 mol) and potassium hydroxide (7.43 g, 0.132 mol) were suspended in absolute ethanol (50 mL) and stirred vigorously at room temperature for thirty minutes. The desoxybenzoin solution was added in one portion, and the yellow suspension was held at reflux, using a Dean-Stark trap to remove generated water, under a nitrogen blanket for 16 hours. The suspension was cooled to room temperature and poured into water (200 mL). The

system was extracted with ethyl acetate (2x150 mL), then the combined organic solution was washed with brine (200 mL), dried over magnesium sulfate, and filtered. The solvents were evaporated under reduced pressure to yield a crude solid. The solid was recrystallized from hot ethanol/water, filtered and washed with water to yield, upon drying, desoxybenzoin keto-oxime as white crystals (17.7 g, 82%); mp 87°-90° C. Mass spectrum, MH⁺=212. High resolution mass spectrum Calc'd. for C₁₄H₁₃NO: 211.0997. Found: 211.0949.

Step 2. Preparation of 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide.

A solution of desoxybenzoin keto-oxime from Step 1 (6.00 g; 28.40 mmol) in anhydrous tetrahydrofuran (THF, 80 mL) was cooled to -20° C. in an oven-dried 250 mL three-neck round-bottom flask equipped with a thermometer, nitrogen gas inlet, rubber septum and provisions for magnetic stirring. To this cold solution, *n*-butyllithium (1.6N in hexanes, 44.4 mL) was added, via syringe, over 35 minutes, such that the reaction temperature remained at or below -10° C. The deep red solution was stirred at -10° C. for 1 hour, warmed to room temperature, then stirred at room temperature for an additional hour. Acetic anhydride (3.2 mL, 34.1 mmol) was added in one portion, and the resulting suspension was stirred without temperature control for 2 hours. Water (100 mL) was added, and the solution was poured into 1N HCl (100 mL) and extracted with ethyl acetate (2x200 mL). The combined organic solution was washed with hydrochloric acid (1N HCl, 100 mL) and brine (100 mL), dried over magnesium sulfate and filtered. The resulting solution was evaporated under reduced pressure to yield a crude oil. The oil was applied to a column of silica gel and eluted with ethyl acetate/hexane (10-50% ethyl acetate) to yield, upon concentration of the appropriate fractions, 5.0 g of 3,4-diphenyl-4-hydroxy-5-hydroxy-5-methylisoxazole. The solid was cooled to 0° C., then dissolved in cold chlorosulfonic acid (15 mL). The brown solution was stirred at 0° C. for 2 hours, then added dropwise to a stirring suspension of ice (200 mL) and dichloromethane (200 mL). The layers were separated, and the organic phase was added directly to a saturated ammonium hydroxide solution (100 mL) at 0° C. This biphasic solution was vigorously stirred at 0° C. for 2 hours, the layers were separated, and the aqueous phase was washed with dichloromethane (50 mL). The combined organic solution was dried over magnesium sulfate, filtered and evaporated under reduced pressure to approximately one-half of its original volume. Crystals formed. The stirred suspension was cooled to 0° C. and held for 30 minutes. The crystals were filtered, washed with cold dichloromethane and dried to yield 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide (2.7 g, 30%); mp 155°-157° C. ¹H NMR (CD₃CN/500 MHz) δ 7.86 (d, J=8.39 Hz, 2H), 7.45 (m, 1H), 7.39 (s, 4H), 7.37 (d, J=8.39 Hz, 2H), 5.70 (s, 2H), 2.46 (s, 3H). Mass Spectrum, MH⁺=315.

Proceeding in a like manner but replacing the anhydrides with other appropriately substituted anhydrides and esters, the following compounds were prepared:

- 1a) 4-[5-ethyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 140°-141° C. ¹H NMR (CDCl₃) δ 7.93 (d, J=8.66, 2 H), 7.28-7.42 (m, 7 H), 4.81 (s, 2H), 2.83 (q, J=7.65 Hz, 2 H), 1.34 (t, J=7.45, 3 H). Mass spectrum M⁺H 329. Anal. Calc'd. for C₁₇H₁₆N₂O₃S: C, 62.18; H, 4.91; N, 8.53; S, 9.76. Found: C, 62.07; H, 4.88; N, 8.42; S, 9.61.
- 1a) 4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 147°-148° C. ¹H NMR (CDCl₃) δ 7.92 (d, J=8.46, 2 H), 7.28-7.44 (m, 7 H), 4.83 (s, 2 H),

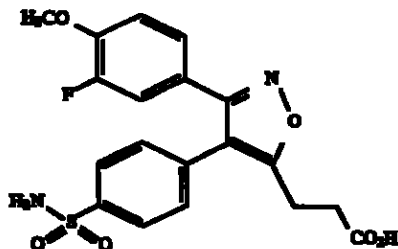
- 2.77 (t, J=7.25, 2 H), 1.71-1.85 (m, 2H), 0.98 (t, J=7.45, 3 H). Anal. Calc'd. for C₁₉H₁₈N₂O₃S: C, 63.14; H, 5.30; N, 8.18; S, 9.36. Found: C, 63.19; H, 5.32; N, 8.23; S, 9.44. Mass spectrum M⁺H 343.
- 1c) 4-[5-isopropyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 166°-168° C. ¹H NMR (CDCl₃) δ 7.93 (d, J=8.46 Hz, 2 H), 7.27-7.40 (m, 7H), 4.80 (s, 2 H), 3.08-3.20 (m, 1 H), 1.36 (d, J=6.58 Hz, 6 H). Mass spectrum M⁺H 343.
- 1d) 4-[5-butyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 129°-131° C. ¹H NMR (CDCl₃) δ 7.93 (d, J=8.46 Hz, 2H), 7.30-7.40 (m, 7H), 4.81 (s, 2H), 2.79 (t, J=7.45, 2H), 1.67-1.79 (m, 2H), 1.30-1.42 (m, 2H), 0.91 (t, J=7.25, 3 H). Anal. Calc'd. for C₂₀H₂₀N₂O₃S: C, 64.02; H, 5.66; N, 7.86; S, 8.99. Found: C, 63.22; H, 5.52; N, 7.51; S, 8.67.
- 1e) 4-[5-isobutyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 159°-160° C. ¹H NMR (CDCl₃) δ 7.93 (d, J=8.46, 2 H), 7.28-7.42 (m, 7H), 4.84 (s, 2H), 2.66 (d, J=7.25 Hz, 2H), 2.08-2.22 (m, 1 H), 0.94 (d, J=6.65 Hz, 6 H). High resolution mass spectrum Calc'd. for C₁₉H₂₀N₂O₃S: 221.0841. Found: 221.0827. Anal. Calc'd. for C₁₉H₂₀N₂O₃S: C, 64.02; H, 5.66; N, 7.86; S, 8.99. Found: C, 63.94; H, 5.65; N, 7.86; S, 8.90.
- 1f) 4-[5-cyclohexyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 191°-193° C. ¹H NMR (CDCl₃) δ 7.94 (d, J=8.46 Hz, 2 H), 7.27-7.41 (m, 7H), 4.85 (s, 2H), 2.62-2.85 (m, 1H), 1.67-1.95 (m, 7 H), 1.22-1.38 (m, 3 H). Mass spectrum M⁺H 383. High resolution mass spectrum Calc'd. for C₂₁H₂₂N₂O₃S: 383.1429. Found: 383.1452.
- 1g) 4-[5-neopentyl-3-phenylisoxazol-4-yl]benzenesulfonamide: ¹H NMR (CDCl₃) δ 7.94 (d, J=8.46, 2 H), 7.26-7.39 (m, 7 H), 4.82 (s, 2 H), 2.71 (s, 2 H), 0.94 (s, 9H). Mass spectrum M⁺H 371.
- 1h) 4-[5-cyclohexylmethyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 151°-153° C. ¹H NMR (CDCl₃) δ 7.93 (d, J=8.46, 2 H), 7.29-7.43 (m, 7H), 4.82 (s, 2H), 2.67 (d, J=7.05 Hz, 2 H), 1.60-1.92 (m, 5 H), 0.85-1.30 (m, 6 H). Mass spectrum M⁺H 397.
- 1i) 4-[5-(4-chlorophenyl)methyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 107°-108° C. ¹H NMR (CDCl₃ and CD₃OD) δ 7.91 (d, J=8.46, 2 H), 7.26-7.42 (m, 9H), 7.14 (d, J=8.46 Hz, 2 H), 4.85 (s, 2 H), 4.10 (s, 2 H). Mass spectrum M⁺H=425. High resolution mass spectrum Calc'd. for C₂₂H₁₇ClN₂O₃S: 425.0727. Found: 425.0736.
- 1j) 4-[5-trifluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide.
- 1k) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 172°-175° C. ¹H NMR (CDCl₃) δ 7.97 (d, J=8.46, 2 H), 7.30-7.50 (m, 7H), 6.72 (t, J=52.57 Hz, 1 H), 4.87 (s, 2H). ¹⁹F NMR (CHCl₃) -116.45 (d, J=63.02 Hz). Mass spectrum M⁺H 351.
- 1l) 4-[5-chloromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide: mp 131°-133° C. ¹H NMR (CDCl₃) δ 7.98 (d, J=8.46, 2 H), 7.34-7.46 (m, 7H), 4.84 (s, 2H), 4.61 (s, 2 H). Mass spectrum M⁺H 349. High resolution mass spectrum for C₁₈H₁₃ClN₂O₃S: 348.0335. Found: 348.0316.
- 1m) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonic acid: mp 260°-269° C. ¹H NMR (CD₃OD) δ 9.03 (s, >1 H exch), 8.42 (d, J=8.06 Hz, 2H), 8.12-8.28 (m, 5 H), 7.97 (d, J=8.26 Hz, 2 H). Mass spectrum M⁺H 316.
- 1n) 4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonic acid: ¹H NMR (CDCl₃ and CD₃OD) δ 7.95-7.78 (m, 2 H), 7.10-7.40 (m, 7H), 2.65-2.78 (m, 2 H), 1.65-1.80 (m, 2H), 0.88-0.99 (m, 3H). Mass spectrum M⁺H 344.

25

1o) 4-[5-methoxymethyl-3-phenylisoxazol-4-yl] benzene sulfonamide: mp 82°-118° C. ¹H NMR (CDCl₃) δ 7.93 (d, J=8.66 Hz, 2 H), 7.31-7.45 (m, 7 H), 4.81 (s, 2 H), 4.51 (s, 2 H), 3.48 (s, 3 H). Mass spectrum M⁺H 345. High resolution mass spectrum Calc'd. for C₁₇H₁₆N₂O₄S: 344.0831. Found: 344.0807.

1p) 4-[5-(3-hydroxypropyl)-3-phenylisoxazol-4-yl] benzene sulfonamide: mp 88°-142° C. ¹H NMR (CDCl₃ and CD₃OD) δ 7.90 (d, J=8.66 Hz, 2 H), 7.26-7.42 (m, 7H), 3.66 (t, J=6.04 Hz, 2 H), 2.91 (t, J=7.45 Hz, 2 H), 1.93-2.02 (m, 2H). Mass spectrum M⁺H 349. High resolution mass spectrum Calc'd. for C₁₈H₁₈N₂O₄S: 358.0987. Found: 358.0958.

EXAMPLE 2



[4-[4-(Aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic Acid

Step 1: Preparation of 1-(3-fluoro-4-methoxyphenyl)-2-phenyl-ethan-1-one.

In a 500 mL, 3-neck round-bottom flask, equipped with a pressure equalizing dropping funnel, thermometer, gas inlet tube and provisions for magnetic stirring, a suspension of aluminum chloride (9.4 g, 70.5 mmol) in a solution of 2-fluoroanisole (6.6 mL, 58.8 mmol) and anhydrous chloroform (200 mL) was cooled to 0° C. under a blanket of dry nitrogen. A solution of phenylacetyl chloride (8.6 mL, 64.7 mmol) in anhydrous chloroform (50 mL) was added to the vigorously stirred suspension over 20 minutes keeping the reaction temperature <5° C. The yellowish solution was stirred at 0° C. for 1 hour, then poured into ice (200 mL) and stirred without temperature control for 16 hours. The layers were separated, and the aqueous layer was extracted with dichloromethane (2x100 mL). The combined organic solution was dried over magnesium sulfate, filtered, and the solvent was evaporated under reduced pressure. The resulting solid was recrystallized from boiling hexane to yield, upon filtration and drying, 12.9 g (90%) of 1-(3-fluoro-4-methoxyphenyl)-2-phenyl-ethan-1-one as white crystals: ¹H NMR (CDCl₃/300 MHz) δ 7.82-7.72 (m, 2H), 7.35-7.24 (m, 5H), 6.98 (dd, J=8.46, 8.26 Hz, 1H), 4.22 (s, 2H), 3.94 (s, 3H). ¹⁹F NMR (CDCl₃/282.2 MHz) -134.875 (m).

Step 2: Preparation of 1-(3-fluoro-4-methoxyphenyl)-2-phenyl-ethan-1-one oxime.

Hydroxylamine hydrochloride (3.7 g, 53.2 mmol) and potassium hydroxide (2.98 g, 53.2 mmol) were suspended in absolute ethanol (25 mL) and vigorously stirred in a 250-mL round-bottom flask equipped with a magnetic stirring bar under a dry nitrogen blanket for 30 minutes. To this, a suspension of 1-(3-fluoro-4-methoxyphenyl)-2-phenyl-ethan-1-one from Step 1 (10.0 g, 40.9 mmol) in toluene (150 mL) was added in one portion. A Dean-Stark trap and reflux condenser were added to the apparatus, and the yellow suspension was warmed to reflux. The solution was maintained at reflux 16 hours, then the suspension was cooled to

26

room temperature. Water (100 mL) was added, and the resulting solution was extracted with ethyl acetate (2x100 mL). The combined organic solution was washed with brine (100 mL), dried over magnesium sulfate and filtered. The resulting solution was evaporated under reduced pressure to yield a crude residue. The residue was crystallized from boiling ethanol/water to yield, upon filtration and drying, 10.0 g (94%) of 1-(3-fluoro-4-methoxyphenyl)-2-phenyl-ethan-1-one oxime as ivory-colored crystals: ¹H NMR (CDCl₃/300 MHz) δ 7.42 (dd, J=12.69, 2.01, 1H), 7.36-7.19 (m, 6H), 6.89 (dd, J=8.66, 8.46 Hz, 1H), 4.16 (s, 2H), 3.88 (s, 3H). ¹⁹F NMR (CDCl₃/282.2 MHz): 135.517 (m).

Step 3: [3-(3-fluoro-4-methoxyphenyl)-4-phenylisoxazol-5-yl]propanoic acid:

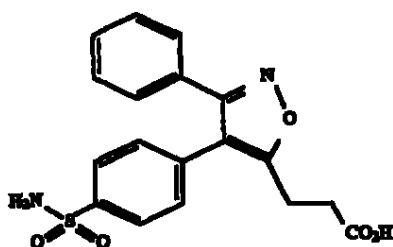
A dry, 250 mL 3-neck round-bottom flask, equipped with a thermometer, magnetic stirring bar, reflux condenser and rubber septum was charged with 1-(3-fluoro-4-methoxyphenyl)-2-phenyl-ethan-1-one oxime from Step 2 (2.00 g, 7.71 mmol) and anhydrous THF (80 mL) under a nitrogen blanket. The solution was cooled to -20° C., and n-butyllithium (1.6N, 12.0 mL) was added, via syringe, over 20 minutes, keeping the reaction temperature <-10° C. The deep red suspension was stirred at -20° C. for 1 hour, warmed to room temperature, and stirred at room temperature for 1 hour. Succinic anhydride (926 mg, 9.26 mmol) was added in one portion, and the yellow reaction was stirred for 16 hours without temperature control. Sulfuric acid (conc., 2.1 mL) was added, and the reaction was warmed to reflux. After 2 hours, the brown mixture was cooled to room temperature, diluted with water (100 mL), and extracted with ether (2x100 mL). The ethereal solution was extracted with dilute sodium hydroxide (2x100 mL), and the combined basic extracts were acidified to pH<2 with hydrochloric acid (conc.). The acidic system was extracted with ether (2x100 mL). This ethereal solution was evaporated under reduced pressure to a residue. The residue was applied to a column of silica gel (200 cc) and eluted (10% methanol in dichloromethane) to yield, upon concentration of the appropriate fractions, a crude solid. The solid was recrystallized from hot ethanol and 0.1N HCl to yield, upon filtration and drying, [3-(3-fluoro-4-methoxyphenyl)-4-phenylisoxazol-5-yl]propanoic acid as ivory colored crystals (367 mg, 14%): mp 129°-131° C. (dec). Mass Spectrum: M⁺H=342. ¹H NMR (CDCl₃/300 MHz) δ 7.39 (m, 3H), 7.22-7.12 (m, 4H), 6.87 (t, J=8.46 Hz, 1H), 3.88 (s, 3H), 3.09 (t, J=8.05 Hz, 2H), 2.80 (t, J=8.05 Hz, 2H). ¹⁹F NMR (CDCl₃/282.2 MHz): -135.466 (m).

Step 4: Preparation of [4-[4-(aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic acid:

[3-(3-fluoro-4-methoxyphenyl)-4-phenylisoxazol-5-yl]propanoic acid from Step 3 (250 mg, 0.73 mmol) and sulfuric acid (1 mL) were dissolved in absolute ethanol (10 mL). The colorless solution was warmed to reflux and held for 16 hours. The solution was cooled to room temperature and diluted with water (20 mL). The aqueous solution was extracted with ether (2x50 mL), and the combined ethereal solution was washed with diluted sodium hydroxide (5%, 2x30 mL) and brine (30 mL). The organic solution was dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield an oil. The oil was cooled to 0° C., and cold chlorosulfonic acid (0° C., 12 mL) was added. The reaction was kept at 0° C. under a nitrogen blanket for 2 hours, and was then carefully poured into ice. The ice was extracted with dichloromethane (2x20 mL), then the organic extract was added directly to a vigorously stirred, 0° C. saturated NH₄OH solution (40 mL). The biphasic reaction was vigorously stirred at 0° C. for 3 hours. The layers were

separated, and the aqueous layer was extracted with dichloromethane (30 mL). The combined organic solution was dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a crude foam. The foam was dissolved in dioxane (30 mL), aqueous sodium hydroxide (10%, 0.9 mL) was added and the solution was heated to reflux for 1 hour. The solution was cooled to room temperature and diluted with water (20 mL). The aqueous solution was extracted with ether (2x30 mL), then the combined ethereal solution was extracted with dilute sodium hydroxide (5%, 2x30 mL). All of the aqueous phases were combined and acidified with hydrochloric acid (conc.) to pH<2. The acidic aqueous phase was extracted with ether (2x30 mL). The final ether solution was dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a crude solid. The solid was recrystallized from ethanol/0.1N HCl to yield, upon filtration and drying, [4-[4-(aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic acid as cream-colored crystals (182 mg, 59%); mp=159°-161° C. (dec). ¹H NMR (CDCl₃/300 MHz) δ 7.91 (d, J=8.66 Hz, 2H), 7.34 (d, J=8.66 Hz, 2H), 7.14 (dd, J=11.88, 2.01 Hz), 7.02 (d, J=8.46 Hz), 6.87 (t, J=8.46 Hz, 1H), 3.86 (s, 3H), 3.03 (t, J=7.45 Hz, 2H), 2.74 (t, J=7.45 Hz, 2H). ¹⁹F NMR (CDCl₃/282.2 MHz): -135.020 (m).

EXAMPLE 3



[4-[4-(Aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]propanoic Acid

Step 1. Preparation of [3,4-diphenylisoxazol-5-yl]propanoic acid.

[3,4-Diphenylisoxazol-5-yl]propanoic acid was prepared in 45% yield from desoxybenzoic oxime (Example 1, Step 1) and succinic anhydride according to the procedure outlined in Example 2, Step 3; mp 123°-125° C. (dec). Anal. Calc'd for C₁₈H₁₅NO₃: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.78; H, 5.18; N, 4.72.

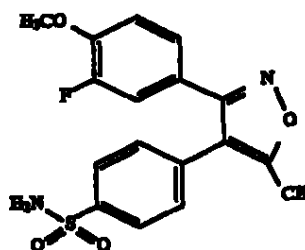
Step 2. Preparation of ethyl [4-[4-(aminosulfonyl)phenyl]-5-phenylisoxazol-5-yl]propanoate:

A solution of [3,4-diphenylisoxazol-5-yl]propanoic acid was treated with ethanol in the presence of a catalytic amount of sulfuric acid to prepare the corresponding ethyl ester which was immediately treated with chlorosulfonic acid followed by ammonia according to the procedure from Example 2, Step 4. The crude sulfonamide was purified by flash chromatography eluting with ethyl acetate/hexane (10-50% ethyl acetate) to yield, upon concentration of the appropriate fractions, ethyl [4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]propanoate as a glassy solid (248 mg, 60%); Mass spectrum: MH⁺=401. ¹H NMR (CDCl₃/300 MHz) δ 7.93 (d, J=8.46 Hz, 2H); 7.41-7.30 (m, 7H), 4.84 (s, 2H), 4.14 (q, J=7.04 Hz, 2H), 3.12 (t, J=7.45 Hz, 2H), 2.81 (t, J=7.45 Hz, 2H), 1.25 (t, J=7.04 Hz, 3H). This material was used directly in the next step without further purification.

Step 3. Preparation of [4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]propanoic acid.

Ethyl [4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]propanoate from Step 2 (198 mg, 0.495 mmol) and aqueous sodium hydroxide (10%, 0.30 mL) were dissolved in dioxane (15 mL). The solution was heated to reflux and held for 16 hours. Upon cooling to room temperature, water (20 mL) was added, and the solution was extracted with ether (2x30 mL). The combined ethereal solution was extracted with dilute sodium hydroxide (5%, 2x30 mL). All of the aqueous phases were combined and acidified with hydrochloric acid (conc.) to pH<2. The acidic aqueous phase was extracted with ether (2x30 mL). The final ether solution was dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a crude solid. Trifluoromethane with dichloromethane yielded crystals. The suspension was cooled to 0° C., filtered, washed with hexane and dried to yield [4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]propanoic acid as a white crystalline solid (135 mg, 73%); mp 207° C. Mass spectrum: MH⁺=373. Anal. Calc'd for C₁₈H₁₅N₂O₅S: C, 58.06; H, 4.33; N, 7.52; S, 8.61. Found: C, 57.87; H, 4.35; N, 7.49; S, 8.54.

EXAMPLE 4



4-[3-(3-Fluoro-4-methoxyphenyl)-5-methylisoxazol-4-yl]benzenesulfonamide

Step 1: Preparation of 3-[3-fluoro-4-methoxyphenyl]-5-methyl-4-phenylisoxazole.

A dry, 250 mL 3-neck round-bottom flask, equipped with a thermometer, magnetic stirring bar, reflux condenser and rubber septum was charged with 1-(3-fluoro-4-methoxyphenyl)-2-phenyl-ethan-1-one oxime (from Example 2, Step 2) (2.50 g, 9.64 mmol) and anhydrous THF (100 mL) under a nitrogen blanket. The solution was cooled to -20° C., and n-butyllithium (1.6N, 15.0 mL) was added via syringe, over 20 minutes, keeping the reaction temperature <-10° C. The deep red suspension was stirred at -20° C. for 1 hour, warmed to room temperature, and stirred at room temperature for 1 hour. Acetic anhydride (1.1 mL, 11.6 mmol) was added in one portion, and the yellow reaction was stirred for 2 hours without temperature control. The reaction was poured into aqueous hydrochloric acid (1N, 100 mL) and extracted with ethyl acetate (2x100 mL). The combined organic solution was washed once each with aqueous hydrochloric acid (1N, 100 mL) and brine (100 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a crude oil. The oil was applied to a column of silica gel (250 ml) and eluted with ethyl acetate/hexane (10-40% ethyl acetate) to yield, upon concentration of the appropriate fractions, 986 mg of 3-(3-fluoro-4-methoxyphenyl)-4-hydroxy-5-hydroxy-4-phenyl-5-methylisoxazole. This intermediate was dissolved in tetrahydrofuran (40 mL). Sulfuric acid (conc., 0.9 mL) was added, and the reaction was warmed to reflux. After one hour, the

solution was cooled to room temperature, diluted with water (50 mL), and extracted with ethyl acetate (2x50 mL). The combined organic solution was washed with aqueous hydrochloric acid (1N, 50 mL), saturated aqueous sodium bicarbonate (2x50 mL) and brine (50 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a crude, dark oil. Washing the oil with 50% dichloromethane in hexane dissolved the compound but did not dissolve the dark impurities. The resulting solution was evaporated under reduced pressure to yield 797 mg (29%) of 3-(3-fluoro-4-methoxyphenyl)-5-methyl-4-phenylisoxazole as a foam. Mass Spectrum: MH⁺=284. Anal. Calc'd for C₁₇H₁₄NO₂F: C, 72.07; H, 4.98; N, 4.94. Found: C, 72.13; H, 4.98; N, 4.92.

Step 2: Preparation of [3-(3-fluoro-4-methoxyphenyl)-5-methylisoxazol-4-yl]benzenesulfonamide:

Chlorosulfonic acid (8 mL) was cooled to 0° C. 3-(3-Fluoro-4-methoxyphenyl)-5-methyl-4-phenylisoxazole from Step 1 (375 mg, 1.32 mmol) was added in one portion. The brown solution was stirred at 0° C. under a nitrogen blanket for 2 hours, then added dropwise to ice (50 mL). The ice was extracted with dichloromethane (2x30 mL), and the organic extracts were added directly to a 0° C. saturated aqueous NH₄OH solution. The biphasic reaction was vigorously stirred at 0° C. for 2 hours, then the layers were separated. The aqueous solution was extracted with dichloromethane, the combined organic solutions were dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a crude solid. The solid was recrystallized from ethanol and water to yield, upon filtration and drying, 4-[3-(3-fluoro-4-methoxyphenyl)-5-methylisoxazol-4-yl]benzenesulfonamide as ivory colored crystals (275 mg, 55%); mp 175° C. (dec). Mass Spectrum: MH⁺=363. Anal. Calc'd for C₁₇H₁₃N₂O₄FS: C, 56.47; H, 4.17; N, 7.73; S, 8.85. Found: C, 56.47; H, 4.19; N, 7.66; S, 8.81.

Proceeding in a like manner but replacing deoxybenzoin with other appropriately substituted ketones, the following compounds were prepared:

4a) 4-[3-(4-chlorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide: mp 162°-164° C. ¹H NMR (CDCl₃) 7.97 (d, 2H, J=8.46 Hz), 7.33-7.26 (m, 7H), 2.48 (s, 3H). Elemental analysis Calc'd for C₁₆H₁₃N₂O₂SCl: C, 55.1; H, 3.76; N, 8.03. Found: C, 55.12; H, 3.78; N, 8.03.

4b) 4-[3-(4-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide: mp 152°-156° C. ¹H NMR (CDCl₃) 2.48 (s, 3H), 4.84 (bs, 2H), 7.04 (t, 1H, J=8.6 Hz), 7.33-7.40 (m, 4H), 7.94 (d, 2H, J=8.4). High resolution mass spectrum Calc'd for C₁₆H₁₂FN₂O₂S: 333.0709. Found: 333.0704.

4c) 4-[3-(3-fluoro-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide: mp 146°-150° C. ¹H NMR (CDCl₃) 2.24 (s, 3H), 2.48 (s, 3H), 4.97 (bs, 2H), 6.93 (t, 1H, J=9.1 Hz), 7.04 (m, 1H), 7.26-7.37 (m, 3H), 7.94 (d, 2H, J=8.3). High resolution mass spectrum Calc'd for C₁₇H₁₅FN₂O₃S: 347.0866. Found: 347.0865. Anal. Calc'd for C₁₇H₁₅FN₂O₃S: C, 58.95; H, 4.37; N, 8.03. Found: C, 58.09; H, 4.47; N, 8.03.

4d) 4-[3-(3-aminosulfonyl-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide.

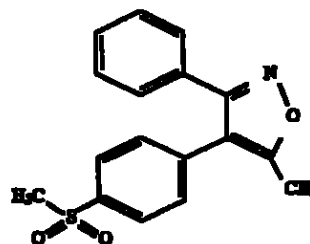
4e) 4-[3-(3-chloro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide: mp 120°-122° C. ¹H NMR (CD₃OD) 2.30 (s, 3H), 2.48 (s, 3H), 4.84 (bs, 2H), 7.11 (m, 1H), 7.33-7.40 (m, 4H), 7.92 (d, 2H, J=8.4). High resolution mass spectrum Calc'd for C₁₇H₁₅FN₂O₂S: 363.0570. Found: 363.0584. Elemental analysis. Calc'd for C₁₇H₁₅ClN₂O₂S: C, 56.28; H, 4.17; N, 7.72. Found: C, 56.02; H, 4.38; N, 7.54.

4f) 4-[5-methyl-3-(3-pyridyl)isoxazol-4-yl]benzenesulfonamide: mp 110°-115° C. (dec). ¹H NMR (CDCl₃) 8.57 (br s, 1H), 8.47 (s, 1H), 7.88, 7.24 (AB quartet, 4H), 7.51-7.41 (m, 2H), 2.43 (s, 3H). Mass spectrum M⁺H 316.

4g) 4-[5-methyl-3-(4-pyridyl)-isoxazol-4-yl]benzenesulfonamide: mp 108°-110° C. (dec). ¹H NMR (CDCl₃) 8.51 (d, 2H, J=6.0 Hz), 7.9 (d, 2H, J=8.46 Hz), 7.30-7.26 (m, 4H), 6.11 (s, 2H), 2.44 (s, 3H). Mass spectrum M⁺H 316. Anal. Calc'd for C₁₅H₁₃N₃O₂SO₂: C, 54.05; H, 4.54; N, 12.62. Found: C, 53.65; H, 4.08; N, 12.42.

4h) 4-[3-(3-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide: mp 130°-136° C. (dec). ¹H NMR (CDCl₃) 7.95 (d, 2H, J=8.5 Hz), 7.33 (d, 2H), 7.33-7.11 (m, 4H), 2.50 (s, 3H). Mass spectrum M⁺H 333. Anal. Calc'd for C₁₆H₁₃N₂O₂SF: C, 57.82; H, 3.94; N, 8.43. Found: C, 57.42; H, 4.57; N, 7.50.

EXAMPLE 5



5-Methyl-4-[4-(methylsulfonyl)phenyl]-3-phenylisoxazole

Step 1. Preparation of 1-phenyl-2-[4-(methylthio)phenyl]ethan-1-one.

This ketone was prepared from the Friedel Crafts acylation of benzene with 4-methylthiophenylacetyl chloride in the presence of aluminum chloride: ¹H NMR (CDCl₃/300 MHz) δ 7.92 (d, J=8.66 Hz, 2H), 7.32-7.22 (m, 7H), 4.24 (s, 2H), 2.51 (s, 3H).

Step 2. Preparation of 1-phenyl-2-[4-(methylthio)phenyl]ethan-1-one oxime.

This oxime was prepared from 1-phenyl-2-[4-(methylthio)phenyl]ethan-1-one (Step 1) and hydroxylamine in 80% yield by the method outlined in Example 1, Step 1: ¹H NMR (CDCl₃/300 MHz) δ 7.54 (d, J=8.66 Hz, 2H), 7.32-7.17 (m, 7H), 4.19 (s, 2H), 2.36 (s, 3H).

Step 3. Preparation of 5-methyl-4-[4-(methylthio)phenyl]-3-phenylisoxazole:

5-Methyl-4-[4-(methylthio)phenyl]-3-phenylisoxazole was prepared in 48% yield from the reaction of 1-phenyl-2-[4-(methylthio)phenyl]ethan-1-one oxime (Step 2) and acetic anhydride according to the procedure outlined in Example 4, Step 1: Mass Spectrum: MH⁺=282. High resolution mass spectrum Calc'd for C₁₇H₁₅NOS: 281.0874. Found: 281.0875. Anal. Calc'd for C₁₇H₁₅NOS: C, 72.57; H, 5.37; N, 4.98; S, 11.39. Found: C, 72.56; H, 5.41; N, 5.00; S, 11.34.

Step 4. Preparation of 5-methyl-4-[4-(methylsulfonyl)phenyl]-3-phenylisoxazole:

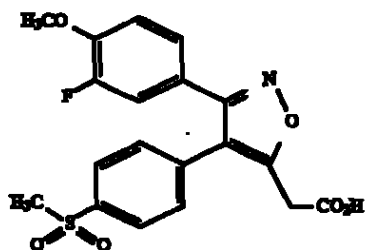
5-Methyl-4-[4-(methylthio)phenyl]-3-phenylisoxazole from Step 3 (100 mg, 0.355 mmol) was dissolved in methanol (20 mL). Oxone® (0.765 g, 1.24 mmol) and water (2 mL) were added, and the suspension was stirred at room

480
444

31

temperature for 2 hours. Water was added (30 mL) and the resulting suspension was cooled to 0° C. and held for 30 minutes whereupon the product crystallized. The product was isolated by filtration, washed with water and dried to yield 5-methyl-4-[4-(methylsulfonyl)phenyl]-3-phenylisoxazole (32 mg, 29%); mp 54°-56° C. Mass Spectrum: MH⁺=320. High resolution mass spectrum Calc'd for C₁₇H₁₅NO₃S: 313.077. Found: 313.078.

EXAMPLE 6



[3-(3-Fluoro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]ethan-1-one oxime

Step 1. Preparation of 1-(3-fluoro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]ethan-1-one.

1-(3-Fluoro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]ethan-1-one was prepared by Friedel Crafts acylation of 2-fluoroanisole with 4-(methylthio)phenylacetyl chloride in the presence of aluminum chloride: ¹H NMR (CDCl₃/300 MHz) δ 7.80-7.70 (m, 2H), 7.24-7.15 (m, 4H), 6.98 (t, J=8.26 Hz), 4.17 (s, 2H), 3.95 (s, 3H), 2.46 (s, 3H). ¹⁹F NMR (CDCl₃/282.2 MHz): -134.804 (m).

Step 2. Preparation of 1-(3-fluoro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]ethan-1-one oxime.

1-(3-Fluoro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]ethan-1-one oxime was prepared in yield by treatment of 1-(3-fluoro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]ethan-1-one from Step 1 with hydroxylamine: ¹H NMR (CDCl₃/300 MHz) δ 7.40 (dd, J=12.69, 2.22 Hz, 1H), 7.30 (d, J=8.66 Hz, 1H), 7.18-7.12 (m, 4H), 6.88 (dd, J=8.66, 8.46 Hz, 1H), 4.10 (s, 2H), 3.87 (s, 3H), 2.43 (s, 3H).

Step 3. Preparation of 3-(3-fluoro-4-methoxyphenyl)-5-methyl-4-[4-(methylthio)phenyl]isoxazole:

3-(3-Fluoro-4-methoxyphenyl)-5-methyl-4-[4-(methylthio)phenyl]isoxazole was prepared in 30% yield from 1-(3-fluoro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]ethan-1-one oxime from Step 2 and acetic anhydride by the procedure described in Example 4. Step 1 and used directly in the next step.

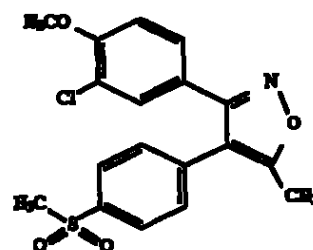
Step 4. Preparation of [3-(3-fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid.

3-(3-Fluoro-4-methoxyphenyl)-5-methyl-4-[4-(methylthio)phenyl]isoxazole (326 mg, 0.99 mmol) was charged to an oven-dried 100 mL 3-neck round-bottom flask equipped with a thermometer, nitrogen inlet, rubber septum and a magnetic stirring bar. Anhydrous THF (35 mL) was added, and the solution was cooled to -78° C. under a dry nitrogen blanket. To this solution, n-butyllithium (1.6N in hexane; 0.74 mL) was added, via syringe over approximately 3 minutes, keeping the reaction temperature <-75° C. The deep red suspension was stirred at -78° C. for 1 hour. Simultaneously, anhydrous tetrahydrofuran (80 mL) was cooled to -78° C. in an oven-dried 250 mL round-bottom flask. This solvent was saturated with carbon dioxide gas.

32

The red reaction solution was quenched into the carbon dioxide-saturated THF. The yellow reaction was warmed to room temperature over 2 hours, then diluted with water (50 mL) and ether (80 mL). The solution was extracted with aqueous sodium hydroxide (5%, 2x50 mL), and the combined aqueous solution was acidified to pH<2 with aqueous hydrochloric acid (conc.). The acidic solution was extracted with dichloromethane (2x50 mL). The combined organic solution was dried over magnesium sulfate, filtered and evaporated under reduced pressure to a crude solid. The solid was dissolved in methanol (20 mL) in a 100 mL round-bottom flask equipped with a magnetic stirring bar and a nitrogen gas inlet. Oxone® (2.13 g, 3.47 mmol) and water (3 mL) were added, the suspension was stirred at room temperature for 2 hours, warmed to reflux and held for an additional 2 hours. Upon cooling to room temperature, water (35 mL) and aqueous hydrochloric acid (6N, 1 mL) were added. The resulting suspension was cooled to 0° C., held for 30 minutes, filtered and washed with cold water to yield, upon drying, [3-(3-fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid as white crystals (173 mg, 43%); mp 89° C. Mass spectrum: MH⁺=406. Anal. Calc'd. for C₁₉H₁₆NO₆S: C, 56.29; H, 3.98; N, 3.46; S, 7.91. Found: C, 56.22; H, 4.00; N, 3.44; S, 7.85.

EXAMPLE 7



3-(3-Chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole

Step 1. Preparation of 3-chloro-4-methoxyacetophenone.

A 5 L round bottomed flask equipped with mechanical stirrer, reflux condenser, constant pressure addition funnel and nitrogen inlet was charged with anhydrous aluminum chloride (281 g, 2.104 mol) and 1 L of ethanol-free chloroform. The solution was maintained at 0° C. with an ice bath while a solution of acetyl chloride (162 g, 2.28 mol) in 300 mL of chloroform was added from the addition funnel over 25 minutes. To this solution was added 2-chloroanisole (250 g, 1.75 mol) in 250 mL of chloroform over 1 hour. The solution was stirred at room temperature for 16 hours and the contents of the flask were poured into a mixture of ice and water. The phases were separated and the aqueous phase extracted with dichloromethane and combined with the original organic phase, dried over anhydrous MgSO₄, filtered and concentrated in vacuo to afford a solid that was crystallized from dichloromethane/hexane to give 3-chloro-4-methoxyacetophenone (246 g, 76%) that was used directly in the next step without further purification.

Step 2. Preparation of 3-chloro-4-methoxyphenylacetic acid.

A mixture of 3-chloro-4-methoxyacetophenone from Step 1 (10.0 g, 54.2 mmol) and boron trifluoride etherate complex (26.6 mL, 0.216 mol) in 20 mL of methanol was added to a suspension of lead tetraacetate (24 g, 54.2 mmol) in 50 mL of toluene. The mixture was stirred at room temperature for

16 hours, treated with 50 mL of water and poured into a separatory funnel. The phases were separated and the aqueous phase washed with toluene. The toluene solution was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to provide an oil that was dissolved in 40 mL of dioxane and treated with excess 2.5N sodium hydroxide solution. The solution was stirred at room temperature for 2 hours and concentrated in vacuo. The residue was extracted with dichloromethane and the aqueous phase acidified with concentrated HCl. The acidic solution was extracted with dichloromethane. The dichloromethane extract was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford pure 3-chloro-4-methoxyphenylacetic acid (9.11 g, 84%) that was used directly in the next step.

Step 3. Preparation of 2-(3-chloro-4-methoxyphenyl)-3-[4-(methylthio)phenyl]-2-propenoic acid.

A mixture of 3-chloro-4-methoxyphenylacetic acid from Step 2 (4.50 g, 22.4 mmol), 4-methylthiobenzaldehyde (2.70 g, 20.4 mmol) and triethylamine (2.8 mL, 20.4 mmol) were dissolved in 40 mL of acetic anhydride and heated to reflux for 3 hours. The solution was cooled to 110° C. and treated cautiously with 70 mL of water and cooled to room temperature, whereupon crystals of 2-(3-chloro-4-methoxyphenyl)-3-[4-(methylthio)phenyl]-2-propenoic acid formed that were isolated by filtration and air dried to afford 3.68 g (75%) of pure compound which was used directly in the next step.

Step 4. Preparation of 1-(3-chloro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]-ethan-1-one.

A solution of 1-(3-chloro-4-methoxyphenyl)-3-[4-(methylthio)phenyl]propenoic acid from Step 3 (5.00 g, 14.9 mmol) and triethylamine (2.20 g, 15.7 mmol) in 50 mL of toluene was cooled to 0° C. and treated with diphenylphosphoryl azide (3.20 g, 14.9 mmol) via syringe. The solution was maintained at 0° C. for 30 minutes and then diluted with water. The phases were separated and the aqueous phase washed with ether. The original toluene solution was combined with the ethereal extract, dried over anhydrous $MgSO_4$, filtered and concentrated to remove the ether. The remaining toluene solution was heated to 115° C. for 90 minutes, treated with tert-butyl alcohol (1.50 g, 16.4 mmol) and maintained at this temperature for an additional 30 minutes. The solution was cooled to 90° C., treated with 1.4 mL of concentrated HCl and cooled to room temperature. The solution was washed with saturated aqueous $NaHCO_3$, and with brine and dried over anhydrous $MgSO_4$, filtered and concentrated to give 1-(3-chloro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]-ethan-1-one as a solid that was used directly in the next step: ^1H NMR ($CDCl_3$ /300 MHz) δ 7.90 (d, $J=8.66$ Hz, 2H), 7.29-7.24 (m, 3H), 7.11 (dd, $J=8.46$, 2.21 Hz, 1H), 6.88 (d, $J=8.46$ Hz, 1H), 4.19 (s, 2H), 3.86 (s, 3H), 2.55 (s, 3H).

Step 5. Preparation of 1-(3-chloro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]-ethan-1-one oxime.

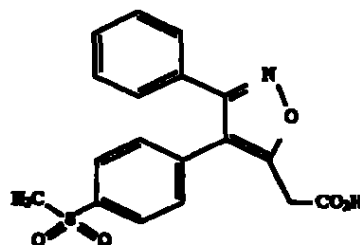
1-(3-Chloro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]-ethan-1-one was prepared in 41% yield from the reaction of 1-(3-chloro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]-ethan-1-one from Step 4 with hydroxylamine by the method outlined in Example 1, Step 1: ^1H NMR ($CDCl_3$ /300 MHz) δ 7.69 (d, $J=2.22$ Hz, 1H), 7.47 (dd, $J=8.66$, 2.22 Hz, 1H), 7.21-7.16 (m, 4H), 6.86 (d, $J=8.66$ Hz, 1H), 4.11 (s, 2H), 3.89 (s, 3H), 2.44 (s, 3H).

Step 6. Preparation of 3-(3-chloro-4-methoxyphenyl)-4-[4-methylsulfonylphenyl]-5-methylisoxazole

3-(3-Chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylthio)phenyl]isoxazole was prepared in 26% yield

from 1-(3-chloro-4-methoxyphenyl)-2-[4-(methylthio)phenyl]-ethan-1-one oxime from Step 5 and acetic anhydride by the method described in Example 4, Step 1 and then oxidized to 3-(3-chloro-4-methoxyphenyl)-5-methyl-4-[4-methylsulfonylphenyl]isoxazole with Oxone® by the method described in Example 5, Step 4: Mass spectrum: $MH^+=384$. High resolution mass spectrum Calc'd. For $C_{18}H_{16}ClNO_4S$: 378.0567. Found: 378.0573.

EXAMPLE 8.



4-[4-(Methylsulfonyl)phenyl]-3-phenylisoxazol-5-yl]acetic Acid

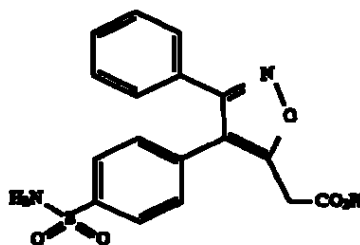
Step 1. Preparation of 4-[4-(methylthio)phenyl]-3-phenylisoxazol-5-yl]acetic acid.

4-[4-(Methylthio)phenyl]-3-phenylisoxazol-5-yl]acetic acid was prepared in 35% yield by carboxylation of 4-[4-(methylthio)phenyl]-5-methyl-3-phenylisoxazole [Example 5, Step 3] according to the procedure detailed in Example 6, Step 4: Mass spectrum: $MH^+=326$. High resolution mass spectrum Calc'd. for $C_{18}H_{15}NO_2S$: 325.0773. Found: 325.0776.

Step 2. Preparation Of 4-[4-(methylsulfonyl)phenyl]-3-phenylisoxazol-5-yl]acetic acid.

4-[4-(Methylsulfonyl)phenyl]-3-phenylisoxazol-5-yl]acetic acid was prepared in 80% yield from 4-[4-(methylthio)phenyl]-3-phenylisoxazol-5-yl]acetic acid (Step 1) by oxidation with Oxone® according to the procedure detailed in Example 5, Step 4: Mass spectrum: $MH^+=326$. High resolution mass spectrum Calc'd. For $C_{18}H_{15}NO_4S$: 358.0749. Found: 358.0769.

EXAMPLE 9



4-[4-(Aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]acetic Acid

Step 1. Preparation of 3,4-diphenyl-5-methylisoxazole.

A solution of desoxybenzoin keto-oxime (Example 1, Step 1) (6.00 g, 28.40 mmol) in anhydrous tetrahydrofuran (80 mL) was cooled to -20° C. in an oven-dried 250 mL three-neck round-bottom flask equipped with a thermometer, nitrogen gas inlet, rubber septum and provisions for magnetic stirring. To this cold solution,

n-butyllithium (1.6N in hexanes, 44.4 mL) was added, via syringe, over 35 minutes, such that the reaction temperature remained at or below -10°C . The deep red solution was stirred at -10°C for 1 hour, warmed to room temperature, then stirred at room temperature for an additional hour. Acetic anhydride (3.2 mL, 34.1 mmol) was added in one portion, and the resulting suspension was stirred without temperature control for 2 hours. Water (100 mL) was added, and the solution was poured into 1N HCl (100 mL) and extracted with ethyl acetate (2x200 mL). The combined organic solution was washed with HCl (1N HCl, 100 mL) and brine (100 mL), dried over anhydrous MgSO_4 and filtered. The resulting solution was concentrated in vacuo to yield a crude oil. The oil was applied to a column of silica gel and eluted with ethyl acetate/hexane (10-50% ethyl acetate) to yield, upon concentration of the appropriate fractions, 5.0 g of 3,4-diphenyl-4-hydroxy-5-methylisoxazole. A 100 mL round bottomed flask equipped with reflux condenser was charged with 3,4-diphenyl-4-hydroxy-5-methylisoxazole (5.00 g, 19.74 mmol), 300 mg of concentrated H_2SO_4 and 30 mL of toluene. The solution was heated to reflux for 1 hour, poured into a separatory funnel and washed with water. The toluene solution was dried over anhydrous MgSO_4 , filtered, and concentrated in vacuo and the residue used directly in the next step without further purification.

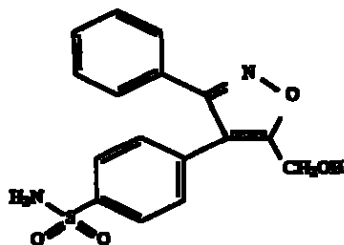
Step 2. Preparation of (3,4-diphenylisoxazol-5-yl)acetic acid:

(3,4-Diphenylisoxazol-5-yl)acetic acid was prepared in 53% yield by carboxylation of 3,4-diphenyl-5-methylisoxazole (Step 1) according to the procedure outlined in Example 6, Step 4: Mass spectrum: $\text{MH}^+=280$. High resolution mass spectrum Calc'd. for $\text{C}_{17}\text{H}_{13}\text{NO}_3$: 280.0894. Found: 280.0897. Anal. Calc'd. for $\text{C}_{17}\text{H}_{13}\text{NO}_3$: C, 73.11; H, 4.69; N, 5.01. Found: C, 72.91; H, 4.73; N, 4.97.

Step 3. Preparation of [4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]acetic acid:

[4-[4-(Aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]acetic acid was prepared in 60% yield by chlorosulfonation followed by ammonolysis of 1-(3,4-diphenylisoxazol-5-yl)acetic acid according to the procedure outlined in Example 2, Step 4: mp 61°C . Mass spectrum: $\text{MH}^+=359$.

EXAMPLE 10

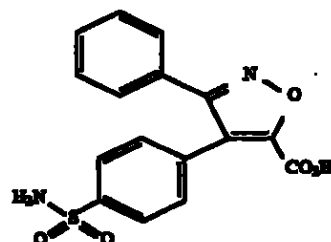


4-[5-Hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide

4-[5-Methyl-3-phenyl-4-yl]benzenesulfonamide (Example 1) (20.965 g, 66.69 mmol) and THF (1.4 L) were cooled to -78°C (dry ice/acetone bath) and a premeasured volume of n-BuLi (167 mL, 266.76 mmol) in a 250 mL round bottomed flask was added via cannula causing the reaction solution to become bright red. After 15 minutes the dry ice/acetone bath was replaced with a NaCl/ice/water bath and the reaction warmed to -5°C over 15 minutes and

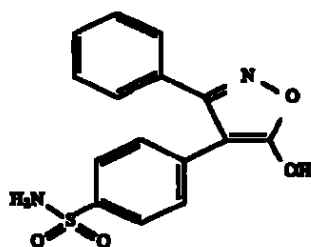
was maintained at -5°C for 30 more minutes. The NaCl/ice/ H_2O bath was replaced with a dry ice/acetone bath and the reaction chilled to -71°C . Oxygen was added via two 14 gauge needles (ca. 4 psi) and a similar outlet provided. Within 10 minutes the reaction, formerly a red suspension, became an ocre-yellow suspension. Oxygen addition was continued for 30 more minutes. The oxygen line and vents were removed and trimethyl phosphite (67 mL, 566.97 mmol) was added via syringe. After 15 minutes, the septum was removed and a solution of HOAc (125 mL) and H_2O (125 mL) was added in one portion causing the solution to become a hazy bright yellow and the reaction temperature to rise to -50°C . The dry ice bath was removed and the reaction was warmed to room temperature. Brine (700 mL) and 1N HCl (134 mL) were added and stirred for 15 minutes. Ethyl acetate (700 mL) was added and the layers were separated in a separatory funnel. The aqueous phase was washed with ethyl acetate (150 mL) and the organic layers combined. The organic layer was washed with water, NaHCO_3 (5x100 mL) and brine, dried over anhydrous MgSO_4 and filtered. The resulting organic phase was diluted with toluene (125 mL) and concentrated in vacuo three times yielding a brown viscous oil. The crude product was purified by flash chromatography (silica gel, 10x18 cm column, hexane/ethyl acetate (1/2) with a step gradient to hexane/ethyl acetate (1/2)) yielding a yellow solid (11.25 g). The product was dissolved in ethyl acetate (500 mL) and acetone (60 mL). Partial concentration of this solution and addition of hexane yielded a yellow solid which was collected by vacuum filtration. This solid was dissolved in a minimum of acetone and added to hot H_2O (800 mL at 70°C) yielding the desired product as a very fine crystalline yellow product (7.89 g, 36%); mp $188^{\circ}\text{--}189^{\circ}\text{C}$. ^1H NMR ($\text{DMSO}-d_6$) δ 7.81 (d, $J=8.26$ Hz, 2H), 7.26-7.55 (m, 9H), 5.77 (t, $J=4.84$, 1H), 4.54 (d, $J=4.84$, 2H). Anal. Calc'd. for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$: C, 58.17; H, 4.27; N, 8.48. Found: C, 58.22; H, 4.31; N, 8.50. Mass spectrum: $\text{M}^+=331$.

EXAMPLE 11



[4-[4-(Aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl]carboxylic Acid

To a solution of 4-[5-hydroxymethyl-3-phenyl-4-yl]benzenesulfonamide (Example 10) (0.64 g, 1.94 mmol) in acetone at -78°C (dry ice/acetone bath) was added carefully Jones reagent (0.7 mL of 2.44M CrO_3 in aqueous H_2SO_4 solution). The reaction was warmed to 0°C and an additional 0.7 mL (2.44M CrO_3 in aqueous H_2SO_4 solution) was added. The reaction was warmed to room temperature and stirred overnight. Isopropanol (2 mL) was added and was stirred for 2 hour. The reaction was diluted with ethyl acetate, washed with H_2O , dried over anhydrous MgSO_4 , filtered through Celite® and concentrated in vacuo yielding a solid. Recrystallization of this solid from toluene yielding the desired product (0.075 g, 11%) as a tan solid: mp 300°C . ^1H NMR ($\text{DMSO}-d_6$) δ 7.70 (d, $J=8.46$ Hz, 2H), 7.06-7.50 (m, 9H).

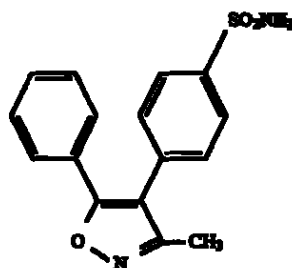
37
EXAMPLE 124-[5-Hydroxy-3-phenyl-4-isoxazolyl]
benzenesulfonamide

Step 1. Preparation of 3,4-diphenylisoxazolin-5-one.

To a stirred solution of the deoxybenzoin oxime (50.59 g, 239 mmol) in anhydrous THF (1 L) in a 2000 mL 2-neck round bottomed flask fitted with septum, under nitrogen atmosphere, and chilled to -78°C . (dry ice/acetone bath) was added $n\text{-BuLi}$ (375 mL of 1.6M in hexanes, 599 mmol) via cannula over 15 minutes. After twenty minutes at -78°C , the dry ice/acetone bath was replaced with a $\text{NaCl}/\text{ice}/\text{H}_2\text{O}$ and the reaction was warmed to 0°C . over 1 hour. The $\text{NaCl}/\text{ice}/\text{H}_2\text{O}$ bath was replaced with a dry ice/acetone bath. When -78°C was reached, the reaction solution was transferred via cannula to a 4 L Erlenmeyer flask filled with 1500 cc of powdered dry ice and the resulting yellow mixture was let stand overnight at room temperature. The clear, straw colored solution was transferred to a 3 L round bottomed flask, and 700 mL of 3N HCl was added. The reaction was heated to reflux for 1 hour and cooled to room temperature. The reaction was diluted with brine (500 mL) and the layers were separated in a separatory funnel. The aqueous layer was extracted with dichloromethane/ethyl acetate (2/1) (400 mL). The organic layers were combined and washed with brine (200 mL), dried over anhydrous MgSO_4 , filtered and concentrated yielding a brown solid. The solid was re-dissolved in warm THF and hexanes were added yielding a fluffy off-white crystalline solid (30.4 g, 54%). A second crop was obtained (12.66 g, 22 %); mp $162^{\circ}\text{--}163^{\circ}\text{C}$. (dec.). This material was suitable for use without further purification.

Step 2. Preparation of 4-[5-hydroxy-3-phenyl-4-yl]benzenesulfonamide.

3,4-Diphenylisoxazolin-5-one from step 1 (15.6 g, 65.75 mmol) was added carefully to ClSO_3H (160 mL) in a 250 mL round bottomed flask chilled in a NaCl/ice bath. After 2 hours, the crude reaction mixture was carefully poured over ice, yielding the crude sulfonyl chloride as a precipitate which was collected by vacuum filtration. The solid was dissolved in dichloromethane yielding two phases which were separated, and the organic phase dried over anhydrous MgSO_4 . This clear pale yellow solution was slowly added to a chilled (0°C) saturated solution of NH_3 in dichloromethane. The resulting suspension was diluted with CH_3OH and was washed with KHSO_4 (0.25M aq soln.). The organic layer was dried over anhydrous MgSO_4 , filtered and concentrated in vacuo yielding a tan solid which was collected by vacuum filtration. This solid was dissolved in a minimum of 1N NaOH solution, filtered, and washed with dichloromethane. The aqueous layer was acidified with concentrated HCl yielding and off-white solid (3.70 g, 18%); mp 207°C . (dec.). ^1H NMR (D_2O with NaOD) δ 7.48 (d, $J=8.46$ Hz, 2 H), 7.38–7.20 (m, 5 H), 7.14, (d, $J=8.26$, 2 H). The methanolic/aqueous KHSO_4 wash phase, upon partial evaporation yielded additional desired product as a tan solid (8.94 g, 43%).

38
EXAMPLE 134-[3-Methyl-5-phenyl-4-isoxazolyl]
benzenesulfonamide

Step 1. Preparation of 1,2-diphenyl-1-butene-3-one oxime.

A solution of 1,2-diphenyl-1-butene-3-one (1.5 g, 7 mmol) in EtOH (15 mL) and was added to a solution of hydroxylamine hydrochloride (500 mg, 7 mmol) and NaHCO_3 (1 g) in water (7 mL). The mixture was heated to reflux for 5 hours at which time thin layer chromatography indicated the reaction was incomplete. Additional hydroxylamine hydrochloride (500 mg, 7 mmol) was added and heating at reflux was continued overnight. The reaction was cooled, poured into water (100 mL) and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and the filtrate concentrated in vacuo. The crude material was chromatographed on silica gel using 5% ethyl acetate in toluene as the eluant to give 450 mg (30%) of the desired oxime as a crystalline solid, mp $138^{\circ}\text{--}141^{\circ}\text{C}$. Anal. Calc'd for $\text{C}_{16}\text{H}_{15}\text{NO}$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.79; H, 6.25; N, 6.09.

Step 2. Preparation of 3,4-diphenyl-5-methylisoxazole

To a solution of oxime from Step 1 (450 mg, 1.9 mmol) and sodium bicarbonate (650 mg, 7.7 mmol) in tetrahydrofuran (6 mL) and water (6 mL) in a vessel wrapped in aluminum foil was added a solution of potassium iodide (1.1 g, 6.6 mmol) and iodine (525 mg, 2 mol) in water (4 mL). The reaction was heated to reflux for 7 hours and stirred at room temperature overnight. Saturated aqueous sodium bisulfite solution (5 mL) was added and the reaction mixture was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and the crude material was isolated after filtration and concentration of the filtrate. Chromatography on silica gel using toluene as the eluant gave 290 mg (57%) of the isoxazole as an oil which crystallized on standing: mp $92^{\circ}\text{--}94^{\circ}\text{C}$. Anal. Calc'd for $\text{C}_{16}\text{H}_{13}\text{NO}$: C, 81.31; H, 5.57; N, 5.95. Found: C, 81.31, H, 5.71; N, 6.18.

Step 3. Preparation of 4-[3-methyl-5-phenyl-4-isoxazolyl]benzenesulfonamide.

A solution of the isoxazole from step 1 (250 mg, 1.1 mmol) in chlorosulfonic acid (1 mL) was stirred at 0°C for 3 hours. The reaction was cautiously added to concentrated ammonium hydroxide (6 mL) in the cold (0°C). The resultant reaction mixture was stirred at 0°C for 1 hour. The reaction was cautiously diluted with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and the filtrate concentrated in vacuo to give the crude product. This material was chromatographed on silica gel using 25% ethyl acetate in toluene as the eluant to give the desired sulfonamide as a crystalline solid (110 mg, 40%); mp $85^{\circ}\text{--}87^{\circ}\text{C}$. Anal. Calc'd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$: C, 61.13; H, 4.49; N, 8.91; S, 10.20. Found: C, 60.88; H, 4.61; N, 8.55; S, 10.40.

458
449

BIOLOGICAL EVALUATION

Rat Carrageenan Foot Pad Edema Test

The carrageenan foot edema test was performed with materials, reagents and procedures essentially as described by Winter, et al., (*Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962)). Male Sprague-Dawley rats were selected in each group so that the average body weight was as close as possible. Rats were fasted with free access to water for over sixteen hours prior to the test. The rats were dosed orally (1 mL) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with vehicle alone. One hour later a subplanter injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline was administered and the volume of the injected foot was measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot was again measured. The average foot swelling in a group of drug-treated animals was compared with that of a group of placebo-treated animals and the percentage inhibition of edema was determined (Otterness and Bliven, *Laboratory Models for Testing NSAIDs, in Non-steroidal Anti-Inflammatory Drugs*, (J. Lombardino, ed. 1985)). The % inhibition shows the % decrease from control paw volume determined in this procedure and the data for selected compounds in this invention are summarized in Table I.

Rat Carrageenan-Induced Analgesia Test

The rat carrageenan analgesia test was performed with materials, reagents and procedures essentially as described by Hargreaves, et al., (*Pain*, 32, 77 (1988)). Male Sprague-Dawley rats were treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan, the rats were placed in a special plexiglass container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty minute period, thermal stimulation was begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell turned off the lamp and timer when light was interrupted by paw withdrawal. The time until the rat withdraws its foot was then measured. The withdrawal latency in seconds was determined for the control and drug-treated groups, and percent inhibition of the hyperalgesic foot withdrawal determined. Results are shown in Table I.

TABLE I

Example	RAT PAW EDEMA % Inhibition ● 10 mg/kg body weight	ANALGESIA % Inhibition ● 10 mg/kg body weight
	29	33
1		

Evaluation of COX-1 and COX-2 activity in vitro

The compounds of this invention exhibited inhibition in vitro of COX-2. The COX-2 inhibition activity of the compounds of this invention illustrated in the Examples was determined by the following methods.

a. Preparation of recombinant COX baculoviruses

Recombinant COX-1 and COX-2 were prepared as described by Glaser et al., [*J. Biochem.*, 305, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 was cloned into a BamHI site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 and COX-2 in a manner similar to the

method of D. B. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses were isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells (2×10^6) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M. D. Summers and G. E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses were purified by three rounds of plaque purification and high titer (10^7 - 10^8 pfu/mL) stocks of virus were prepared. For large scale production, SF9 insect cells were infected in 10 liter fermentors (0.5×10^6 /mL) with the recombinant baculovirus stock such that the multiplicity of infection was 0.1. After 72 hours the cells were centrifuged and the cell pellet homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate was centrifuged at 10,000×G for 30 minutes, and the resultant supernatant was stored at -80° C. before being assayed for COX activity.

b. Assay for COX-1 and COX-2 activity

COX activity was assayed as PGE₂ formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme were incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and home with the addition of arachidonic acid (10 µM). Compounds were pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after ten minutes at 37° C./room temperature by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. The PGE₂ formed was measured by standard ELISA technology (Cayman Chemical). Results are shown in Table II.

TABLE II

Example	COX-2 ID ₅₀ µM	COX-1 ID ₅₀ µM
1	<0.1	>100
1a	<0.1	17.4
1b	<0.1	13.2
1c	<0.1	6.2
1d	<0.1	23.8
1e	<0.1	37.7
1f	0.2	34
1g	<0.1	>100
1h	<0.1	4.7
1i	<0.1	8.6
1k	<0.1	>100
1l	<0.1	30.7
1m	1.5	>100
1n	31	>100
1o	<0.1	>100
1p	0.1	>100
2	0.9	17.4
3	2.6	0.6
4	3	>100
4a	<0.1	90.5
4b	<0.1	>100
4c	<0.1	66.3
4d	<0.1	44
4e		
4f	2	>100
4g	>100	>100
5	4.0	>100
6	33.7	>100
7	86.7	>100
8	>100	>100
9	1.4	>100

38

TABLE II-continued

Example	COX-2 ID ₅₀ μ M	COX-1 ID ₅₀ μ M
10	0.2	>100
11	35	
12	2.5	>100
13	<0.1	6.4

Also embraced within this invention is a class of pharmaceutical compositions comprising one or more compounds of Formula I in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier materials") and, if desired, other active ingredients. The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and composition may, for example, be administered intravenously, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compound that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredient in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably between about 1 to 20 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

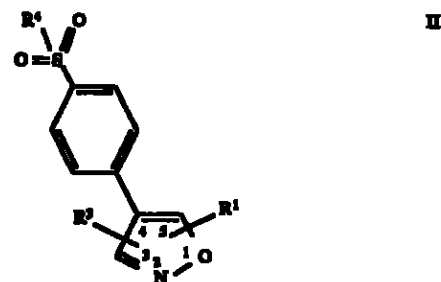
For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxy-propylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn

oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

What is claimed is:

1. A compound of Formula II



wherein R^1 is selected from alkyl, carboxyalkyl, alkoxyalkyl, aminocarbonyl, aminocarbonylalkyl, alkoxyalkyl, carboxyl, alkoxy, haloalkoxy, aralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, aryloxyalkyl, arylthioalkyl, hydroxyl, amino, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxyalkyl, alkoxyalkyl, alkylaminocarbonyloxyalkyl, alkoxyalkyl, and alkylaminocarbonylthioalkyl;

wherein R^2 is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxyalkyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfonyl, alkylsulfonyl, aminoalkoxy, halo, alkoxy and alkylthio; and wherein R^4 is selected from lower alkyl, hydroxyl, and amino;

or a pharmaceutically-acceptable salt thereof.

2. A compound of claim 1 wherein R^1 is selected from hydroxyl, amino, lower alkyl, lower carboxyalkyl, lower alkoxyalkyl, aminocarbonyl, carboxyl, lower aminocarbonylalkyl, lower alkoxyalkyl, lower alkoxy, lower haloalkoxy, lower aralkoxy, lower cycloalkylalkoxy, lower alkylthio, lower aralkylthio, lower cycloalkylalkylthio, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower aryloxyalkyl, lower arylthioalkyl, lower hydroxyalkyl, lower haloalkyl, lower cycloalkyl, lower cycloalkylalkyl, lower aralkyl, halo, lower alkylamino, lower aralkylamino, lower N-alkyl-N-aralkylamino, lower N-alkyl-N-cycloalkylalkylamino, lower arylcarbonyloxyalkyl, lower alkoxyalkyl, lower alkoxyalkyl, lower alkylaminocarbonyloxyalkyl, lower alkoxyalkyl, and lower alkylaminocarbonylthioalkyl; wherein R^2 is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfonyl, lower alkyl, cyano, carboxyl, lower alkoxyalkyl, lower haloalkyl,

4/26/5

39

43

hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy, lower alkylsulfonyl, aminosulfonyl, and lower alkylthio; and wherein R^4 is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

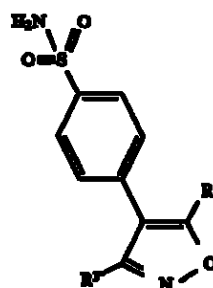
3. A compound of claim 2 wherein R^1 is selected from hydroxyl, lower alkyl, carboxyl, lower carboxyalkyl, lower aminocarbonylalkyl, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower arylalkoxyalkyl, lower arylthioalkyl, lower haloalkyl, lower hydroxyalkyl, cycloalkyl, cycloalkylalkyl, and aralkyl; wherein R^2 is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfinyl, lower alkyl, cyano, carboxyl, lower alkoxyalkyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy, aminosulfonyl, and lower alkylthio; and wherein R^4 is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

4. A compound of claim 3 wherein R^1 is selected from hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, carboxyl, carboxypropyl, carboxymethyl, carboxyethyl, benzyl, phenethyl, aminocarbonylmethyl, methoxycarbonylmethyl, methoxycarbonylethyl, methoxymethyl, benzylloxymethyl, phenylethoxymethyl, methylthiomethyl, benzylthiomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, phenyloxymethyl, phenylthiomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxymethyl, hydroxypropyl, hydroxyethyl, cyclohexyl, cyclobutyl, cyclopentyl, cycloheptyl, cyclohexylmethyl, cyclohexylethyl, cyclobutylethyl, cyclopentylmethyl, cycloheptylpropyl, and lower aralkyl selected from benzyl and phenylethyl, wherein the phenyl ring is optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, methyl, and methoxy; wherein R^2 is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, and 1-cyclopentenyl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfinyl, ethylsulfinyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, aminosulfonyl, methylthio, ethylthio, butylthio, and hexylthio; and wherein R^4 is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

5. The compound of claim 4 which is 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

44

6. A compound of Formula III



III

wherein R^1 is selected from hydroxyl, alkyl, carboxyalkyl, aminocarbonylalkyl, alkoxyalkyl, carboxyl, alkoxy, haloalkoxy, aralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, arylalkoxyalkyl, arylthioalkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxyalkoxyalkyl, alkylaminocarbonyloxyalkyl, alkoxyalkoxyalkyl, and alkylaminocarbonylthioalkyl; and

wherein R^2 is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxyalkyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfinyl, aminosulfonyl, halo, alkoxy and alkylthio; or a pharmaceutically-acceptable salt thereof.

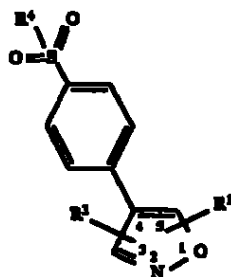
7. A compound of claim 6 wherein R^1 is selected from hydroxyl, lower alkyl, carboxyl, lower carboxyalkyl, lower aminocarbonylalkyl, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower arylalkoxyalkyl, lower arylthioalkyl, lower haloalkyl, lower hydroxyalkyl, lower cycloalkyl, and aralkyl; wherein R^2 is selected from cycloalkyl, cycloalkenyl, and aryl; and wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfinyl, aminosulfonyl, lower alkyl, cyano, carboxyl, lower alkoxyalkyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy and lower alkylthio; or a pharmaceutically-acceptable salt thereof.

8. A compound of claim 7 wherein R^1 is selected from hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, carboxyl, carboxypropyl, carboxymethyl, carboxyethyl, benzyl, phenethyl, aminocarbonylmethyl, methoxycarbonylmethyl, methoxycarbonylethyl, methoxymethyl, benzylloxymethyl, phenylethoxymethyl, methylthiomethyl, benzylthiomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, phenyloxymethyl, phenylthiomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, dichloroethyl, dichloropropyl, hydroxymethyl, hydroxypropyl, hydroxyethyl, cyclohexyl, cyclobutyl, cyclopentyl, cycloheptyl,

40

cyclohexylmethyl, cyclohexylethyl, cyclobutylethyl, cyclopentylmethyl, cycloheptylpropyl, and lower aralkyl selected from phenylethyl and benzyl optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, methyl, and methoxy; and wherein R^2 is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, and 1-cyclopentenyl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfinyl, ethylsulfinyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, aminomethyl, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, methylthio, aminosulfonyl, ethylthio, butylthio, and hexylthio; or a pharmaceutically-acceptable salt thereof.

9. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Formula II



wherein R^1 is selected from alkyl, carboxyalkyl, alkoxycarbonyl, aminocarbonyl, aminocarbonylalkyl, alkoxycarbonylalkyl, carboxyl, alkoxy, haloalkoxy, aralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, arylalkoxyalkyl, arylthioalkyl, hydroxyl, amino, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxycarbonyloxyalkyl, alkylaminocarbonyloxyalkyl, alkoxycarbonylthioalkyl, and alkylaminocarbonylthioalkyl;

wherein R^2 is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxycarbonyl, haloalkyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminalkyl, nitro, alkoxyalkyl, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, halo, alkoxy and alkylthio; and wherein R^4 is selected from lower alkyl, hydroxyl, and amino;

or a pharmaceutically-acceptable salt thereof.

10. A pharmaceutical composition of claim 9 wherein R^1 is selected from hydroxyl, amino, lower alkyl, lower

carboxyalkyl, lower alkoxycarbonyl, aminocarbonyl, carboxyl, lower aminocarbonylalkyl, lower alkoxycarbonylalkyl, lower alkoxy, lower haloalkoxy, lower aralkoxy, lower cycloalkylalkoxy, lower alkylthio, lower aralkylthio, lower cycloalkylalkylthio, lower alkoxyalkyl, lower aralkoxyalkyl, lower aralkylthioalkyl, lower aralkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower arylalkoxyalkyl, lower arylthioalkyl, lower hydroxyalkyl, lower haloalkyl, lower cycloalkyl, lower cycloalkylalkyl, lower aralkyl, halo, lower alkylamino, lower aralkylamino, lower N-alkyl-N-aralkylamino, lower N-alkyl-N-cycloalkylalkylamino, lower arylcarbonyloxyalkyl, lower alkoxycarbonyloxyalkyl, lower alkylaminocarbonyloxyalkyl, lower alkoxycarbonylthioalkyl, and lower alkylaminocarbonylthioalkyl; wherein R^2 is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfinyl, lower alkyl, cyano, carboxyl, lower alkoxycarbonyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminalkyl, nitro, halo, lower alkoxy, lower alkylsulfonyl, aminosulfonyl, and lower alkylthio; and wherein R^4 is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

11. A pharmaceutical composition of claim 10 wherein R^1 is selected from hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, carboxyl, carboxypropyl, carboxymethyl, carboxyethyl, benzyl, phenethyl, aminocarbonylmethyl, methoxycarbonylmethyl, methoxycarbonylethyl, methoxycarbonylmethyl, benzylloxymethyl, phenylethylloxymethyl, methylthiomethyl, benzylthiomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, phenylloxymethyl, phenylthiomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxymethyl, hydroxylpropyl, hydroxyethyl, cyclohexyl, cyclobutyl, cyclopentyl, cycloheptyl, cyclohexylethyl, cyclohexylethyl, cyclobutylethyl, cyclopentylethyl, cycloheptylpropyl, and lower aralkyl selected from benzyl and phenylethyl, wherein the phenyl ring is optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, methyl, and methoxy; wherein R^2 is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, and 1-cyclopentenyl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfinyl, ethylsulfinyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, aminosulfonyl, methylthio, ethylthio, butylthio, and hexylthio; and wherein R^4 is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

12. A pharmaceutical composition of claim 11 wherein said compound is 4-[5-methyl-3-phenyl-isoxazol-4-yl] benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

alkoxycarbonyloxyalkyl, alkylaminocarbonyloxyalkyl, alkoxycarbonylthioalkyl, and alkylaminocarbonylthioalkyl;



10

19

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or a pharmaceutically-acceptable salt thereof.

15 15. A method of claim 14 wherein R^1 is selected from hydroxyl, amino, lower alkyl, lower carboxyalkyl, lower alkoxy carbonyl, aminocarbonyl, carboxyl, lower aminocarbonylalkyl, lower alkoxy carbonylalkyl, lower alkoxy, lower haloalkoxy, lower aralkoxy, lower cycloalkylalkoxy, lower alkylthio, lower aralkylthio, lower cycloalkylalkylthio, lower alkoxyalkyl, lower aralkoxyalkyl, lower alkylthioalkyl, lower aralkylthioalkyl, lower alkylaminoalkyl, lower arylalkoxyalkyl, lower arylthioalkyl, lower hydroxyalkyl, lower haloalkyl, lower cycloalkyl, lower cycloalkylalkyl, lower aralkyl, halo, lower alkylamino, lower aralkylamino, lower N-alkyl-N-aralkylamino, lower N-alkyl-N-cycloalkylalkylamino, lower arylcarbonyloxyalkyl, lower alkoxy carbonyloxyalkyl, lower alkylaminocarbonyloxyalkyl, lower alkoxy carbonylthioalkyl, and lower alkylaminocarbonylthioalkyl; wherein R^2 is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfanyl, lower alkyl, 25 cyano, carbonyl, lower alkoxy carbonyl, lower haloalkyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, lower arylamino, lower aminoalkyl, nitro, halo, lower alkoxy, lower alkylsulfonyl, aminosulfonyl, and lower alkylthio; and wherein R^4 is selected from methyl, 40 hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

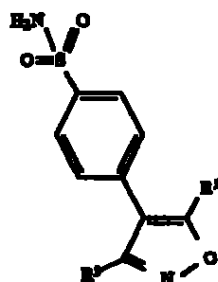
16. A method of claim 15 wherein R^1 is selected from hydroxyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, neopentyl, hexyl, carbonyl, carboxypropyl, 45 carboxymethyl, carboxyethyl, benzyl, phenethyl, aminocarbonylmethyl, methoxycarbonylmethyl, methoxycarbonylethyl, methoxymethyl, benzoyloxymethyl, phenylethoxymethyl, methylthiomethyl, benzylthiomethyl, N-methylaminomethyl, N,N-dimethylaminomethyl, 50 phenyloxymethyl, phenylthiomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, 55 hydroxylmethyl, hydroxylpropyl, hydroxyethyl, cyclohexyl, cyclobutyl, cyclopentyl, cycloheptyl, cyclohexylmethyl, cyclohexylethyl, cyclobutylethyl, cyclopentylmethyl, cycloheptylpropyl, and lower alkyl selected from benzyl and phenylethyl, wherein the phenyl 60 ring is optionally substituted at a substitutable position with fluoro, chloro, bromo, iodo, methyl, and methoxy; wherein R^2 is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, and 1-cyclopentenyl; 65 wherein R^3 is optionally substituted at a substitutable position with one or more radicals independently selected from trifluoromethoxy, N-methylamino, N,N-dimethylamino,

49

N-ethylamino, N,N-dipropylamino, N-butylamino, N-methyl-N-ethylamino, phenylamino, N-methyl-N-phenylamino, methylsulfinyl, ethylsulfinyl, methyl, ethyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, fluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, hydroxymethyl, amino, nitro, fluoro, chloro, bromo, iodo, methoxy, ethoxy, propoxy, n-butoxy, pentoxy, hexyloxy, methylenedioxy, aminosulfonyl, methylthio, ethylthio, butylthio, and hexylthio; and wherein R⁴ is selected from methyl, hydroxyl and amino; or a pharmaceutically-acceptable salt thereof.

17. A method of claim 16 wherein said compound is 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

18. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to said inflammation or inflammation-associated disorder, a therapeutically-effective amount of a compound of Formula III



wherein R¹ is selected from hydroxyl, alkyl, carboxyalkyl, aminocarbonylalkyl, alkoxy, haloalkoxy, aralkoxy, cycloalkylalkoxy, alkylthio, aralkylthio, cycloalkylalkylthio, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, aralkylthioalkyl, alkylaminoalkyl, arylalkoxyalkyl, arylthioalkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aralkyl, halo, alkylamino, aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-cycloalkylalkylamino, arylcarbonyloxyalkyl, arylcarbonylthio, alkoxy, alkoxyalkyl, alkylaminocarbonyloxyalkyl, alkoxy, alkoxyalkyl, and alkylaminocarbonylthioalkyl; and

wherein R² is selected from cycloalkyl, cycloalkenyl, and aryl; wherein R³ is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, cyano, carboxyl, alkoxy, haloalkoxy, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, aminoalkyl, nitro, alkoxyalkyl, alkylsulfinyl, aminosulfonyl, halo, alkoxy and alkylthio; or a pharmaceutically-acceptable salt thereof.

19. A method of claim 14 for use in treatment of inflammation.

20. A method of claim 14 for use in treatment of an inflammation-associated disorder.

21. A method of claim 20 wherein the inflammation-associated disorder is arthritis.

22. A method of claim 20 wherein the inflammation-associated disorder is pain.

23. A method of claim 20 wherein the inflammation-associated disorder is fever.

50

24. The compound of claim 4 selected from compounds, or their pharmaceutically acceptable salts, of the group consisting of

- 4-[5-ethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-isopropyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-butyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-isobutyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-cyclohexyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-neopentyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-cyclohexylmethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-(4-chlorophenyl)methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-trifluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-chloromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;
- 4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;
- 4-[5-methoxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[5-(3-hydroxypropyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 4-[3-(4-chlorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
- 4-[3-(4-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
- 4-[3-(3-fluoro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
- 4-[3-(3-aminosulfonyl-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
- 4-[3-(3-chloro-4-methylphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
- 4-[3-(3-fluorophenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
- 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- [4-(4-(aminosulfonyl)phenyl)-3-phenylisoxazol-5-yl]carboxylic acid;
- 4-[5-hydroxy-3-phenyl-4-isoxazolyl]benzenesulfonamide;
- 4-[3-methyl-5-phenyl-isoxazol-4-yl]benzenesulfonamide;
- 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;
- 4-[3-(3-fluoro-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;
- [3-(3-chloro-4-methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)isoxazol-5-yl]acetic acid;
- 5-methyl-4-[4-(methylsulfonyl)phenyl]-3-phenylisoxazole;
- 3-(3-chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;
- [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]acetic acid;

4/145

51

[4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl] propanoic acid;

ethyl [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoate;

[3-(3-fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid; and

[4-[4-(aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic acid.

25. The compound of claim 4 which is 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl] benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

26. A pharmaceutical composition of claim 11 wherein said compound is selected from compounds, or their pharmaceutically-acceptable salts, of the group consisting of

4-[5-ethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isopropyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-butyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isobutyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-cyclohexyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-neopentyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-cyclohexylmethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-(4-chlorophenyl)methyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-trifluoromethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-difluoromethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-chloromethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-methoxymethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-(3-hydroxypropyl)-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[3-(4-chlorophenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;

4-[3-(4-fluorophenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;

4-[3-(3-fluoro-4-methylphenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;

4-[3-(3-aminosulfonyl-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-chloro-4-methylphenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;

4-[3-(3-fluorophenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;

4-[5-hydroxymethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

[4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl] carboxylic acid;

4-[5-hydroxy-3-phenyl-4-isoxazolyl] benzenesulfonamide;

4-[3-methyl-5-phenyl-isoxazol-4-yl] benzenesulfonamide;

52

4-[5-methyl-3-phenyl-isoxazol-4-yl] benzenesulfonamide;

4-[3-(3-fluoro-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

[3-(3-chloro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid;

5-methyl-4-[4-(methylsulfonyl)phenyl]-3-phenyl-isoxazole;

3-(3-chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;

[4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl] acetic acid;

[4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl] propanoic acid;

ethyl [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoate;

[3-(3-fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid; and

[4-[4-(aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic acid.

27. A pharmaceutical composition of claim 11 wherein said compound is 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

28. A method of claim 16 wherein said compound is selected from compounds, or their pharmaceutically-acceptable salts, of the group consisting of

4-[5-ethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isopropyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-butyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isobutyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-cyclohexyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-neopentyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-cyclohexylmethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-(4-chlorophenyl)methyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-trifluoromethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-difluoromethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-chloromethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-methoxymethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-(3-hydroxypropyl)-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[3-(4-chlorophenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;

4-[3-(4-fluorophenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;

4-[3-(3-fluoro-4-methylphenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;

4-[3-(3-aminosulfonyl-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

44

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51

[4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl] propanoic acid;

ethyl [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoate;

[3-(3-fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid; and

[4-[4-(aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic acid.

25. The compound of claim 4 which is 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl] benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

26. A pharmaceutical composition of claim 11 wherein said compound is selected from compounds, or their pharmaceutically-acceptable salts, of the group consisting of

4-[5-ethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isopropyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-butyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isobutyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-cyclohexyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-neopentyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-cyclohexylmethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-(4-chlorophenyl)methyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-trifluoromethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-difluoromethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-chloromethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-methoxymethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-(3-hydroxypropyl)-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[3-(4-chlorophenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;

4-[3-(4-fluorophenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;

4-[3-(3-fluoro-4-methylphenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;

4-[3-(3-aminosulfonyl-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

4-[3-(3-chloro-4-methylphenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;

4-[3-(3-fluorophenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;

4-[5-hydroxymethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

[4-[4-(aminosulfonyl)phenyl]-3-phenylisoxazol-5-yl] carboxylic acid;

4-[5-hydroxy-3-phenyl-4-isoxazolyl] benzenesulfonamide;

4-[3-methyl-5-phenyl-isoxazol-4-yl] benzenesulfonamide;

52

4-[5-methyl-3-phenyl-isoxazol-4-yl] benzenesulfonamide;

4-[3-(3-fluoro-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

[3-(3-chloro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid;

5-methyl-4-[4-(methylsulfonyl)phenyl]-3-phenyl-isoxazole;

3-(3-chloro-4-methoxyphenyl)-5-methyl-4-[4-(methylsulfonyl)phenyl]isoxazole;

[4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl] acetic acid;

[4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl] propanoic acid;

ethyl [4-[4-(aminosulfonyl)phenyl]-3-phenyl-isoxazol-5-yl]propanoate;

[3-(3-fluoro-4-methoxyphenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl]acetic acid; and

[4-[4-(aminosulfonyl)phenyl]-3-(3-fluoro-4-methoxyphenyl)isoxazol-5-yl]propanoic acid.

27. A pharmaceutical composition of claim 11 wherein said compound is 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

28. A method of claim 16 wherein said compound is selected from compounds, or their pharmaceutically-acceptable salts, of the group consisting of

4-[5-ethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isopropyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-butyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

4-[5-isobutyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-cyclohexyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-neopentyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-cyclohexylmethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-(4-chlorophenyl)methyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-trifluoromethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-difluoromethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-chloromethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-propyl-3-phenylisoxazol-4-yl]benzenesulfonic acid;

4-[5-methoxymethyl-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[5-(3-hydroxypropyl)-3-phenylisoxazol-4-yl] benzenesulfonamide;

4-[3-(4-chlorophenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;

4-[3-(4-fluorophenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;

4-[3-(3-fluoro-4-methylphenyl)-5-methyl-isoxazol-4-yl] benzenesulfonamide;

4-[3-(3-aminosulfonyl-4-methoxyphenyl)-5-methyl-isoxazol-4-yl]benzenesulfonamide;

463 457

ANEXO 2

(19)



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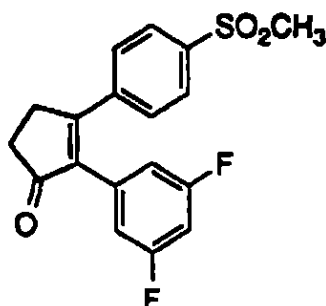
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(54) 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one useful as an inhibitor of cyclooxygenase-2

(57) The invention encompasses the novel compound A, 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one, pharmaceutical compositions and use of the compound in the preparation of medicaments for the treatment of cyclooxygenase-2 mediated diseases.



Compound A

Description

BACKGROUND OF THE INVENTION

This invention relates to methods of treating cyclooxygenase mediated diseases and certain pharmaceutical compositions therefor.

Non-steroidal, antiinflammatory drugs exert most of their antiinflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Initially, only one form of cyclooxygenase was known, this corresponding to cyclooxygenase-1 (COX-1) or the constitutive enzyme, as originally identified in bovine seminal vesicles. More recently the gene for a second inducible form of cyclooxygenase, cyclooxygenase-2 (COX-2) has been cloned, sequenced and characterized initially from chicken, murine and human sources. This enzyme is distinct from the COX-1 which has been cloned, sequenced and characterized from various sources including the sheep, the mouse and man. The second form of cyclooxygenase, COX-2, is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. As prostaglandins have both physiological and pathological roles, we have concluded that the constitutive enzyme, COX-1, is responsible, in large part, for endogenous basal release of prostaglandins and hence is important in their physiological functions such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, we have concluded that the inducible form, COX-2, is mainly responsible for the pathological effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Thus, a selective inhibitor of COX-2 will have similar antiinflammatory, antipyretic and analgesic properties to a conventional non-steroidal antiinflammatory drug, and in addition would inhibit hormone-induced uterine contractions and have potential anti-cancer effects, but will have a diminished ability to induce some of the mechanism-based side effects. In particular, such a compound should have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

Furthermore, such a compound will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labour, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's disease, for decreasing bone loss particularly in postmenopausal women (i.e. treatment of osteoporosis) and for the treatment of glaucoma.

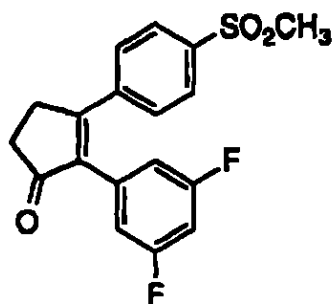
A brief description of the potential utility of cyclooxygenase-2 inhibitors is given in an article by John Vane, *Nature*, Vol. 367, pp. 215-216, 1994, and in an article in *Drug News and Perspectives*, Vol. 7, pp- 501-512, 1994.

SUMMARY OF THE INVENTION

The invention encompasses the novel compound 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one, pharmaceutical compositions and use of the compound in the preparation of medicaments for the treatment of cyclooxygenase-2 mediated diseases.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect the invention encompasses the compound 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one:



Compound A

In a second aspect the invention encompasses pharmaceutical compositions useful for the treatment of COX-2 mediated diseases comprising 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopentan-1-one and a pharmaceutically acceptable carrier.

In a third aspect the invention encompasses pharmaceutical compositions comprising 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopentan-1-one and a pharmaceutically acceptable carrier.

In a fourth aspect the invention encompasses the use 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopentan-1-one in the preparation of a medicament for the treatment of COX-2 mediated diseases.

In a further aspect compositions, methods of treatment, and uses involving oral administration is preferred.

In a further aspect, compositions, methods of treatment and use involving once a day or twice a day administration is preferred.

The following abbreviations have the indicated meanings:

AA	= arachidonic acid
CHO	= chinese hamster ovary
CMC	= 1-cyclohexyl-3-(2-morpholinoethyl) carbodimidemetho-p-toluenesulfonate
COX	= cyclooxygenase
DMF	= N,N-dimethylformamide
HBSS	= Hanks balanced salt solution
HEPES	= N-[2-Hydroxyethyl]piperazine-N ¹ -[2-ethanesulfonic acid]
HWB	= human whole blood
LPS	= lipopolysaccharide
mCPBA	= meta-chloroperoxybenzoic acid
MMPP	= magnesium monoperoxyphthalate
NSAID	= non-steroidal anti-inflammatory drug
PDC	= pyridinium dichromate
r.t.	= room temperature
THF	= tetrahydrofuran

The Compound A is useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries following surgical and dental procedures. In addition, such a compound may inhibit cellular neoplastic transformations and metastatic tumour growth and hence can be used in the treatment of cancer, such as cancer of the colon. Compound A may also be of use in the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in diabetic retinopathy and tumour angiogenesis.

Compound A will also inhibit prostanoïd-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labour, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's disease, for decreasing bone loss particularly in postmenopausal women (i.e. treatment of osteoporosis), and for treatment of glaucoma.

By virtue of its high cyclooxygenase-2 (COX-2) activity and/or its specificity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1), Compound A will prove useful as an alternative to conventional non-steroidal antiinflammatory drugs (NSAID'S) particularly where such non-steroidal antiinflammatory drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; those prior to surgery or taking anticoagulants.

Similarly, Compound A, will be useful as a partial or complete substitute for conventional NSAID'S in preparations wherein NSAIDS are presently co-administered with other agents or ingredients. Thus in further aspects, the invention encompasses pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined above comprising a non-toxic therapeutically effective amount of the compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetaminophen or phenacetin; a potentiator including caffeine; an H₂-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephedrine, naphazoline, xylometazoline, propylhexedrine, or levodroxyephedrine, an antitussive including codeine, hydrocodone, caramiphen, carbapentane, or dextromethorphan; a prostaglandin including misoprostol, enprostil, rioprostil, omoprostol or roseprostol; a diuretic; a sedating or non-sedating antihistamine. In addition the invention encompasses a method of treating cyclooxygenase mediated diseases comprising: administration to a patient in need of such treatment a non-toxic therapeutically effective amount of the compound A, optionally co-administered with one or more of such ingredients as listed immediately

467 461

above.

For the treatment of any of these cyclooxygenase mediated diseases Compound A may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

As indicated above, pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredients may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to 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. 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, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, 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. They may also be coated by the technique described in the U.S. Patent 4,256,106; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, 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 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 polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. 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 anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredients in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or sus-

50

pension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. 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, fatty acids such as oleic acid find use in the preparation of injectables.

Compound A may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures 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.

For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound A are employed. (For purposes of this application, topical application shall include mouth washes and gargles.) Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

Other suitable formulations are set forth in U.S. Patent No. 5,474,995. We have found the following oral formulations to be of particular value:

Rapilac® - In view of the above mentioned characteristics, 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one is particularly well suited for a rapid dissolving sublingual formulation. For example, due to the lack of GI side-effects, the agent need not be taken with a large amount of water. Suitable Rapilac® formulations and methods of making same are disclosed in US 4,305,502, US 4,371,516, US 4,470,202, US 4,758,598, US 4,754,597, US 5,048,618 and US 5,188,882, all of which are hereby incorporated by reference.

As mentioned elsewhere in this specification, we have found 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one to possess a surprising combination of attributes. Not only is compound A active, potent, safe and effective at modest oral dosages of 10 to 250 mg of agent per day, but in addition Compound A possesses a half-life in humans of sufficient length that one or two oral doses of 10 to 250 mg of active agent per day will provide effective safe and anti-inflammatory treatment over a 24 hour period. Such agents are particularly useful in the treatment of chronic indications, such as rheumatoid and osteo arthritis as well as Alzheimer's Disease.

Oral and intravenous dosage levels for agent 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one are of the order of from about 10 to 250 mg per patient once or twice a day.

The amount of active agent 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 10 to 250 mg of 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 may typically contain 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 125 or 250 mg of active agent.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination and the type and severity of the particular disease undergoing therapy. For many patients, a dosage range of 10 to 50 or 60 to 120 mg once or twice a day is preferred.

For long term therapy, such as in the treatment of chronic diseases including rheumatoid arthritis, osteoarthritis or Alzheimer disease, a dosage of 10 to 50 or 60 to 120 mg once or twice a day is preferred. More particularly, for the treatment of osteoarthritis, a dosage of 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 mg once or twice a day is preferred, whereas for the treatment of rheumatoid arthritis, 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 mg once or twice a day is preferred. For the treatment of non-chronic indications such as headache or post-operative swelling and pain, 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 mg once or twice a day is preferred.

Accordingly, in one aspect the invention is directed to a unit dose oral form which comprises from 10 to 250 mg of the cyclooxygenase inhibitor, for example, 10 to 50 or 60 to 120 mg.

In another aspect this invention is directed to a pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition suitable for once or twice a day oral administration, said composition comprising a 10 to 250 mg of 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one, and a pharmaceutical carrier therefor.

Within this aspect there is a first genus of compositions comprising 10 to 50 mg of 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.

Within this aspect there is a second genus of compositions comprising 60 to 120 mg of 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.

The amount of active ingredient 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 10 mg to 250 mg 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 will generally contain between from about 10 mg to about 250 mg of an active ingredient, typically 10 mg, 25 mg, 50 mg, 100 mg, 125 mg, or 250 mg.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Assays for determining Biological Activity

The compound A can be tested using the following assays to determine their cyclooxygenase-2 inhibiting activity.

INHIBITION OF CYCLOOXYGENASE ACTIVITY

Whole cell assays for COX-2 and COX-1 using CHO transfected cell lines

Chinese hamster ovary (CHO) cell lines which have been stably transfected with an eukaryotic expression vector pCDNAIII containing either the human COX-1 or COX-2 cDNA's are used for the assay. These cell lines are referred to as CHO [hCOX-1] and CHO [hCOX-2], respectively. For cyclooxygenase assays, CHO[hCOX-1] cells from suspension cultures and CHO[hCOX-2] cells prepared by trypsinization of adherent cultures are harvested by centrifugation (300 x g, 10 min) and washed once in HBSS containing 15 mM HEPES, pH 7.4, and resuspended in HBSS, 15 mM HEPES, pH 7.4, at a cell concentration of 1.5×10^6 cells/ml. Drugs to be tested are dissolved in DMSO to 66.7-fold the highest test drug concentration. Compounds are typically tested at 8 concentrations in duplicate using serial 3-fold serial dilutions in DMSO of the highest drug concentration. Cells (0.3×10^6 cells in 200 μ l) are preincubated with 3 μ l of the test drug or DMSO vehicle for 15 min at 37°C. Working solutions of peroxide-free AA (5.5 μ M and 110 μ M AA for the CHO [hCOX-1] and CHO [COX-2] assays, respectively) are prepared by a 10-fold dilution of a concentrated AA solution in ethanol into HBSS containing 15 mM HEPES, pH 7.4. Cells are then challenged in the presence or absence of drug with the AA-HBSS solution to yield a final concentration of 0.5 μ M AA in the CHO[hCOX-1] assay and a final concentration of 10 μ M AA in the CHO[hCOX-2] assay. The reaction is terminated by the addition of 10 μ l 1 N HCl followed by neutralization with 20 μ l of 0.5 N NaOH. The samples are centrifuged at 300 x g at 4°C for 10 min, and an aliquot of the clarified supernatant is appropriately diluted for the determination of PGE₂ levels using an enzyme-linked immunoassay for PGE₂ (Correlate PGE₂ enzyme immunoassay kit, Assay Designs, Inc.). Cyclooxygenase activity in the absence of test compounds is determined as the difference in PGE₂ levels of cells challenged with arachidonic acid versus the PGE₂ levels in cells mock-challenged with ethanol vehicle. Inhibition of PGE₂ synthesis by test compounds is calculated as a percentage of the activity in the presence of drug versus the activity in the positive control samples.

Assay of COX-1 Activity from U937 cell microsomes

U 937 cells are pelleted by centrifugation at 500 x g for 5 min and washed once with phosphate-buffered saline and repelleted. Cells are resuspended in homogenization buffer consisting of 0.1 M Tris-HCl, pH 7.4, 10 mM EDTA, 2 μ g/ml leupeptin, 2 μ g/ml soybean trypsin inhibitor, 2 μ g/ml aprotinin and 1 mM phenyl methyl sulfonyl fluoride. The cell suspension is sonicated 4 times for 10 sec and is centrifuged at 10,000 x g for 10 min at 4° C. The supernatant is centrifuged at 100,000 x g for 1 hr at 4° C. The 100,000 x g microsomal pellet is resuspended in 0.1 M Tris-HCl, pH 7.4, 10 mM EDTA to approximately 7 mg protein/ml and stored at -80° C.

Microsomal preparations are thawed immediately prior to use, subjected to a brief sonication, and then diluted to a protein concentration of 125 μ g/ml in 0.1 M Tris-HCl buffer, pH 7.4 containing 10 mM EDTA, 0.5 mM phenol, 1 mM reduced glutathione and 1 μ M hematin. Assays are performed in duplicate in a final volume of 250 μ l. Initially, 5 μ l of DMSO vehicle or drug in DMSO are added to 20 μ l of 0.1 M Tris-HCl buffer, pH 7.4 containing 10 mM EDTA in wells of a 96-deepwell polypropylene titre plate. 200 μ l of the microsomal preparation are then added and pre-incubated for 15 min at room temperature before addition of 25 μ l of 1 M arachidonic acid in 0.1 M Tris-HCl and 10 mM EDTA, pH 7.4. Samples are incubated for 40 min at room temperature and the reaction is stopped by the addition of 25 μ l of 1 N HCl. Samples are neutralized with 25 μ l of 1 N NaOH prior to quantitation of PGE₂ content by radioimmunoassay (DuPont-NEN or Amersham assay kits). Cyclooxygenase activity is defined as the difference between PGE₂ levels in samples incubated in the presence of arachidonic acid and ethanol vehicle.

Assay of the activity of purified human COX-2

The enzyme activity is measured using a chromogenic assay based on the oxidation of N,N,N',N'-tetramethyl-p-phenylenediamine (TMPD) during the reduction of PGG₂ to PGH₂ by COX-2 (Copeland et al. (1994) Proc. Natl. Acad. Sci. 91, 11202-11208).

475 464

Recombinant human COX-2 is purified from Sf9 cells as previously described (Percival et al (1994) Arch. Biochem. Biophys. 15, 111-118). The assay mixture (180 μ L) contains 100 mM sodium phosphate, pH 6.5, 2 mM genapol X-100, 1 μ M hematin, 1 mg/ml gelatin, 80-100 units of purified enzyme (One unit of enzyme is defined as the amount of enzyme required to produce an O.D. change of 0.001/min at 610 nm) and 4 μ L of the test compound in DMSO. The mixture is pre-incubated at room temperature (22°C) for 15 minutes prior to initiation of the enzymatic reaction by the addition of 20 μ L of a sonicated solution of 1 mM arachidonic acid (AA) and 1 mM TMPD in assay buffer (without enzyme or hematin). The enzymatic activity is measured by estimation of the initial velocity of TMPD oxidation over the first 38 sec of the reaction. A non-specific rate of oxidation is observed in the absence of enzyme (0.007 - 0.010 O.D. /min) and is subtracted before the calculation of the % inhibition. IC₅₀ values are derived from 4-parameter least squares non-linear regression analysis of the log-dose vs % inhibition plot.

HUMAN WHOLE BLOOD ASSAY

Rationale

Human whole blood provides a protein and cell-rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as selective COX-2 inhibitors. Studies have shown that normal human blood does not contain the COX-2 enzyme. This is consistent with the observation that COX-2 inhibitors have no effect on PGE₂ production in normal blood. These inhibitors are active only after incubation of human whole blood with LPS, which induces COX-2. This assay can be used to evaluate the inhibitory effect of selective COX-2 inhibitors on PGE₂ production. As well, platelets in whole blood contain a large amount of the COX-1 enzyme. Immediately following blood clotting, platelets are activated through a thrombin-mediated mechanism. This reaction results in the production of thromboxane B₂ (TxB₂) via activation of COX-1. Thus, the effect of test compounds on TxB₂ levels following blood clotting can be examined and used as an index for COX-1 activity. Therefore, the degree of selectivity by the test compound can be determined by measuring the levels of PGE₂ after LPS induction (COX-2) and TxB₂ following blood clotting (COX-1) in the same assay.

Method

A. COX-2 (LPS-induced PGE₂ production)

Fresh blood is collected in heparinized tubes by venipuncture from both male and female volunteers. The subjects have no apparent inflammatory conditions and have not taken any NSAIDs for at least 7 days prior to blood collection. Plasma is immediately obtained from a 2mL blood aliquot to use as blank (basal levels of PGE₂). The remaining blood is incubated with LPS (100 μ g/ml final concentration, Sigma Chem, #L-2630 from E. coli; diluted in 0.1% BSA (Phosphate buffered saline) for 5 minutes at room temperature. Five hundred μ L aliquots of blood are incubated with either 2 μ L of vehicle (DMSO) or 2 μ L of a test compound at final concentrations varying from 10nM to 30 μ M for 24 hours at 37°C. At the end of the incubation, the blood is centrifuged at 12,000 x g for 5 minutes to obtain plasma. A 100 μ L aliquot of plasma is mixed with 400 μ L of methanol for protein precipitation. The supernatant is obtained and is assayed for PGE₂ using a radioimmunoassay kit (Amersham, RPA#530) after conversion of PGE₂ to its methyl oximate derivative according to the manufacturer's procedure.

B. COX-1 (Clotting-Induced TxB₂ production)

Fresh blood is collected into vacutainers containing no anticoagulants. Aliquots of 500 μ L are immediately transferred to siliconized microcentrifuge tubes preloaded with 2 μ L of either DMSO or a test compound at final concentrations varying from 10nM to 30 μ M. The tubes are vortexed and incubated at 37°C for 1 hour to allow blood to clot. At the end of incubation, serum is obtained by centrifugation (12,000 x g for 5 min.). A 100 μ L aliquot of serum is mixed with 400 μ L of methanol for protein precipitation. The supernatant is obtained and is assayed for TxB₂ using a enzyme immunoassay kit (Cayman, #519031) according to the manufacturer's instruction.

RAT PAW EDEMA ASSAY

Protocol

Male Sprague-Dawley rats (150-200 g) are fasted overnight and are given po, either vehicle (1% methocel or 5% Tween 80) or a test compound. One hr later, a line is drawn using a permanent marker at the level above the arde in one hind paw to define the area of the paw to be monitored. The paw volume (V₀) is measured using a plethysmometer

(Ugo-Basile, Italy) based on the principle of water displacement. The animals are then injected subplantarily with 50 μ l of 1% carrageenan solution in saline (FMC Corp, Maine) into the paw using an insulin syringe with a 25-gauge needle (i.e. 500 μ g carrageenan per paw). Three hr later, the paw volume (V_3) is measured and the increases in paw volume ($V_3 - V_0$) are calculated. The animals are sacrificed by CO₂ asphyxiation and the absence or presence of stomach lesions scored. Data is compared with the vehicle-control values and percent inhibition calculated. All treatment groups are coded to eliminate observer bias.

NSAID-INDUCED GASTROPATHY IN RATS

Rationale

The major side effect of conventional NSAIDs is their ability to produce gastric lesions in man. This action is believed to be caused by inhibition of Cox-1 in the gastrointestinal tract. Rats are particularly sensitive to the actions of NSAIDs. In fact, rat models have been used commonly in the past to evaluate the gastrointestinal side effects of current conventional NSAIDs. In the present assay, NSAID-induced gastrointestinal damage is observed by measuring fecal ⁵¹Cr excretion after systemic injection of ⁵¹Cr-labeled red blood cells. Fecal ⁵¹Cr excretion is a well-established and sensitive technique to detect gastrointestinal integrity in animals and man.

Methods

Male Sprague Dawley rats (150 - 200 g) are administered orally a test compound either once (acute dosing) or b.i.d. for 5 days (chronic dosing). Immediately after the administration of the last dose, the rats are injected via a tail vein with 0.5 mL of ⁵¹Cr-labeled red blood cells from a donor rat. The animals are placed individually in metabolism cages with food and water ad lib. Feces are collected for a 48 h period and ⁵¹Cr fecal excretion is calculated as a percent of total injected dose. ⁵¹Cr-labeled red blood cells are prepared using the following procedures. Ten mL of blood is collected in heparinized tubes via the vena cava from a donor rat. Plasma is removed by centrifugation and replenished with equal volume of HBSS. The red blood cells are incubated with 400 Ci of sodium ⁵¹chromate for 30 min. at 37° C. At the end of the incubation, the red blood cells are washed twice with 20 mL HBSS to remove free sodium ⁵¹chromate. The red blood cells are finally reconstituted in 10 mL HBSS and 0.5 mL of the solution (about 20 Ci) is injected per rat.

PROTEIN-LOSING GASTROPATHY IN SQUIRREL MONKEYS

Rationale

Protein-losing gastropathy (manifested as appearance of circulating cells and plasma proteins in the GI tract) is a significant and dose-limiting adverse response to standard non-steroidal anti-inflammatory drugs (NSAIDs). This can be quantitatively assessed by intravenous administration of ⁵¹CrCl₃ solution. This isotopic ion can avidly bind to cell and serum globins and cell endoplasmic reticulum. Measurement of radioactivity appearing in feces collected for 24 h after administration of the isotope thus provides a sensitive and quantitative index of protein-losing gastropathy.

Methods

Groups of male squirrel monkeys (0.8 to 1.4 kg) are treated by gavage with either 1% methocel or 5% Tween 80 in H₂O vehicles, (2mL/kg b.i.d.) or test compounds at doses from 1 - 100 mg/kg b.i.d. for 5 days. Intravenous ⁵¹Cr (5Ci/kg in 1 mL/kg phosphate buffer saline (PBS)) is administered 1 h after the last drug/vehicle dose, and feces collected for 24 h in a metabolism cage and assessed for excreted ⁵¹Cr by gamma-counting. Venous blood is sampled 1 h and 8 h after the last drug dose, and plasma concentrations of drug measured by RP-HPLC.

LPS-Induced Pyrexia in Conscious Rats

Male Sprague-Dawley rats (150 - 200 g) were fasted for 16 - 18 h before use. At approximately 9:30 a.m., the animals were placed temporarily in plexiglass restrainers and their baseline rectal temperature was recorded using a flexible temperature probe (YSI series 400) connected to a digital thermometer (Model 08502, Cole Parmer). The same probe and thermometer were used for all animals to reduce experimental error. The animals were returned to their cages after the temperature measurements. At time zero, the rats were injected intraperitoneally with either saline or LPS (2 mg/kg, Sigma Chem) and the rectal temperature was remeasured at 5, 6 and 7 h following LPS injection. After the measurement at 5 h, when the increase in temperature had reached a plateau, the LPS-injected rats were given either the vehicle (1% methocel) or a test compound orally to determine whether the compound could reverse the

4/2 466

pyrexia. Percent reversal of the pyrexia was calculated using the rectal temperature obtained at 7 h in the control (vehicle-treated) group as the reference (zero reversal) point. Complete reversal of pyrexia to the pre-LPS baseline value is taken as 100%.

8 LPS-Induced Pyrexia in Conscious Squirrel Monkeys

Temperature probes were surgically implanted under the abdominal skin in a group of squirrel monkeys (*Saimiri sciureus*) (1.0 - 1.7 kg). This allows for the monitoring of body temperature in conscious, unrestrained monkeys by a telemetric sensing system (Data Sciences International, Minnesota). The animals were fasted and were placed in individual cages for acclimatization 13 - 14 h before use. Electronic receivers were installed on the side of the cages which pick up signals from the implanted temperature probes. At approximately 9:00 a.m. on the day of the experiment, the monkeys were restrained temporarily in training chairs and were given a bolus i.v. injection of LPS (6 mg/kg, dissolved in sterile saline). The animals were returned to their cages and body temperature was recorded continuously every 5 min. Two h after injection of LPS, when the body temperature had increased by 1.5 - 2° C, the monkeys were dosed orally with either vehicle (1% methocel) or a test compound (3 mg/kg). One hundred minutes later, the difference between the body temperature and the baseline value was determined. Percent inhibition was calculated taking the value in the control group as 0% inhibition.

20 Acute Inflammatory Hyperalgesia Induced by Carrageenan in Rats

Experiments were performed using male Sprague Dawley rats (90-110g). Hyperalgesia to mechanical compression of the hind paw was induced by intraplantar injection of carrageenan (4.5 mg into one hind paw) 3 h previously. Control animals received an equivalent volume of saline (0.15 ml intraplantar). A test compound (0.3-30 mg/kg, suspended in 0.5% methocel in distilled water) or vehicle (0.5% methocel) was administered orally (2ml/kg) 2 h after carrageenan. The vocalisation response to compression of the hind paw was measured 1 h later using a Ugo Basile algesiometer.

Statistical analysis for carrageenan-induced hyperalgesia was performed using one-way ANOVA (BMDP Statistical Software Inc.). Hyperalgesia was determined by subtracting the vocalisation threshold in saline injected rats from that obtained in animals injected with carrageenan. Hyperalgesia scores for drug-treated rats were expressed as a percentage of this response. ID₅₀ values (the dose producing 50% of the maximum observed response) were then calculated by nonlinear least squares regression analysis of mean data using GraFit (Erithacus Software).

Adjuvant-Induced Arthritis in Rats

Seventy, 6.5-7.5 week old, female Lewis rats (body weight ~146-170 g) were weighed, ear marked, and assigned to groups (a negative control group in which arthritis was not induced, a vehicle control group, a positive control group administered indomethacin at a total daily dose of 1 mg/kg and four groups administered with a test compound at total daily doses of 0.10-3.0 mg/kg) such that the body weights were equivalent within each group. Six groups of 10 rats each were injected into a hind paw with 0.5 mg of *Mycobacterium butyricum* in 0.1 ml of light mineral oil (adjuvant), and a negative control group of 10 rats was not injected with adjuvant. Body weights, contralateral paw volumes (determined by mercury displacement plethysmography) and lateral radiographs (obtained under Ketamine and Xylazine anesthesia) were determined before (day -1) and 21 days following adjuvant injection, and primary paw volumes were determined before (day -1) and on days 4 and 21 following adjuvant injection. The rats were anesthetized with an intramuscular injection of 0.03 - 0.1 ml of a combination of Ketamine (87 mg/kg) and Xylazine (13 mg/kg) for radiographs and injection of adjuvant. The radiographs were made of both hind paws on day 0 and day 21 using the Faxitron (45 kVp, 30 seconds) and Kodak X-OMAT TL film, and were developed in an automatic processor. Radiographs were evaluated for changes in the soft and hard tissues by an investigator who was blinded to experimental treatment. The following radiographic changes were graded numerically according to severity: increased soft tissue volume (0-4), narrowing or widening of joint spaces (0-5) subchondral erosion (0-3), periosteal reaction (0-4), osteolysis (0-4) subluxation (0-3), and degenerative joint changes (0-3). Specific criteria were used to establish the numerical grade of severity for each radiographic change. The maximum possible score per foot was 28. A test compound at total daily doses of 0.1, 0.3, 1, and 3 mg/kg/day, indomethacin at a total daily dose of 1 mg/kg/day, or vehicle (0.5% methocel in sterile water) were administered per os b.i.d. beginning post injection of adjuvant and continuing for 21 days. The compounds were prepared weekly, refrigerated in the dark until used, and vortex mixed immediately prior to administration.

Two-factor ('treatment' and 'time') analysis of variance with repeated measures on 'time' were applied to the % changes for body weight and foot volumes and to the rank-transformed radiographic total scores. A *post hoc* Dunnett's test was conducted to compare the effect of treatments to vehicle. A one-way analysis of variance was applied to the thymic and spleen weights followed by the Dunnett's test to compare the effect of treatments to vehicle. Dose-response

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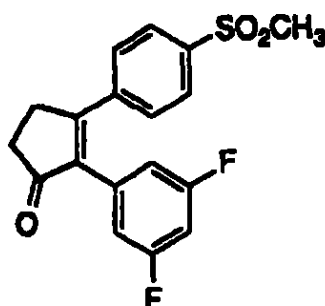
curves for % inhibition in foot volumes on days 4, 14 and 21 were fitted by a 4-parameter logistic function using a non-linear least squares' regression. ID₅₀ was defined as the dose corresponding to a 50% reduction from the vehicle and was derived by interpolation from the fitted 4-parameter equation.

Representative Biological Data

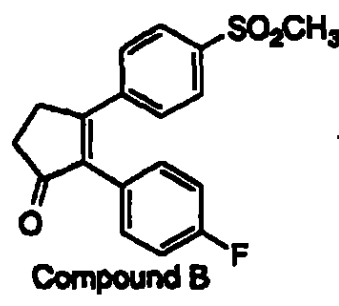
Compounds of the present invention are inhibitors of COX-2 and are thereby useful in the treatment of COX-2 mediated diseases as enumerated above. The activities of compound A against cyclooxygenase may be seen in the representative results shown below in the Table. In the assays, inhibition is determined by measuring the amount of a prostaglandin synthesized in the presence and absence of a putative inhibitor. The IC₅₀ values represent the concentration of putative inhibitor required to lower prostaglandin synthesis to 50% of that obtained as compared to the uninhibited control. The ED₅₀ values in the rat paw edema assay represent the dose of compound required to reduce edema formation by 50% as compared to the vehicle control. Shown also are the corresponding biological activities of Compound B, which compound is disclosed in WO 95/00501, Example 7 and US 5,536,752.

Table

Assay



Compound A



Compound B

COX-2:

CHO Cells

.03 μM

.02 μM

Whole Blood

.45 μM

.12 μM

COX-1

CHO cells

>50 μM

17

Whole Blood

77 μM

4.4 μM

U937 microsomes

11 μM

0.45 μM

Rat Paw edema (ED₅₀)

2.6 mg/kg

3.0 mg/kg

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

- (i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C;
- (ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (800-4000 pascals: 4.5-30 mm Hg) with a bath temperature of up to 60°C;
- (iii) the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only;
- (iv) melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;
- (v) the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data;

56

(vi) yields are given for illustration only;

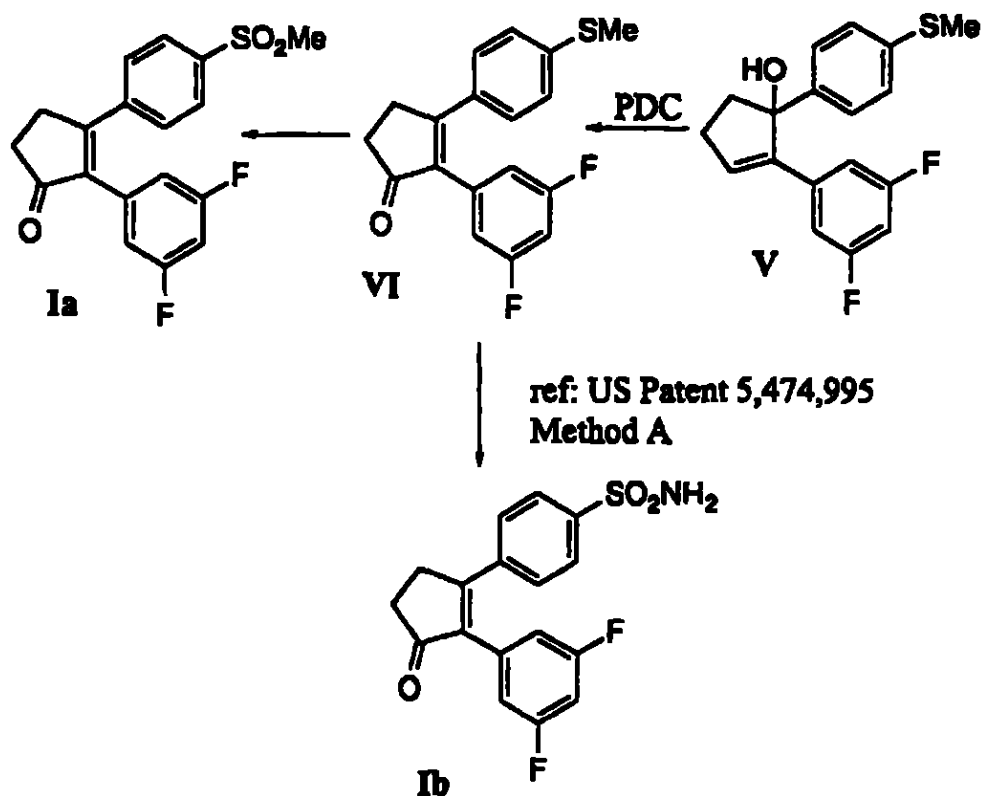
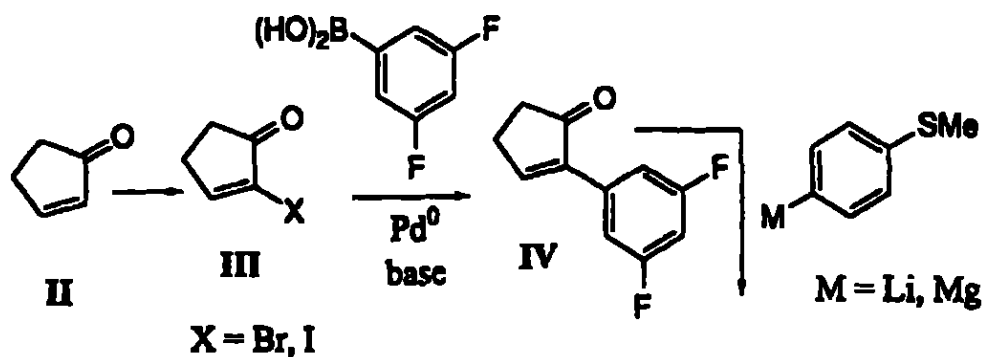
(vii) when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: In addition "Ar" signifies an aromatic signal;

(viii) chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), M.P. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

Compound A can be prepared according to the following methods Methods of Synthesis

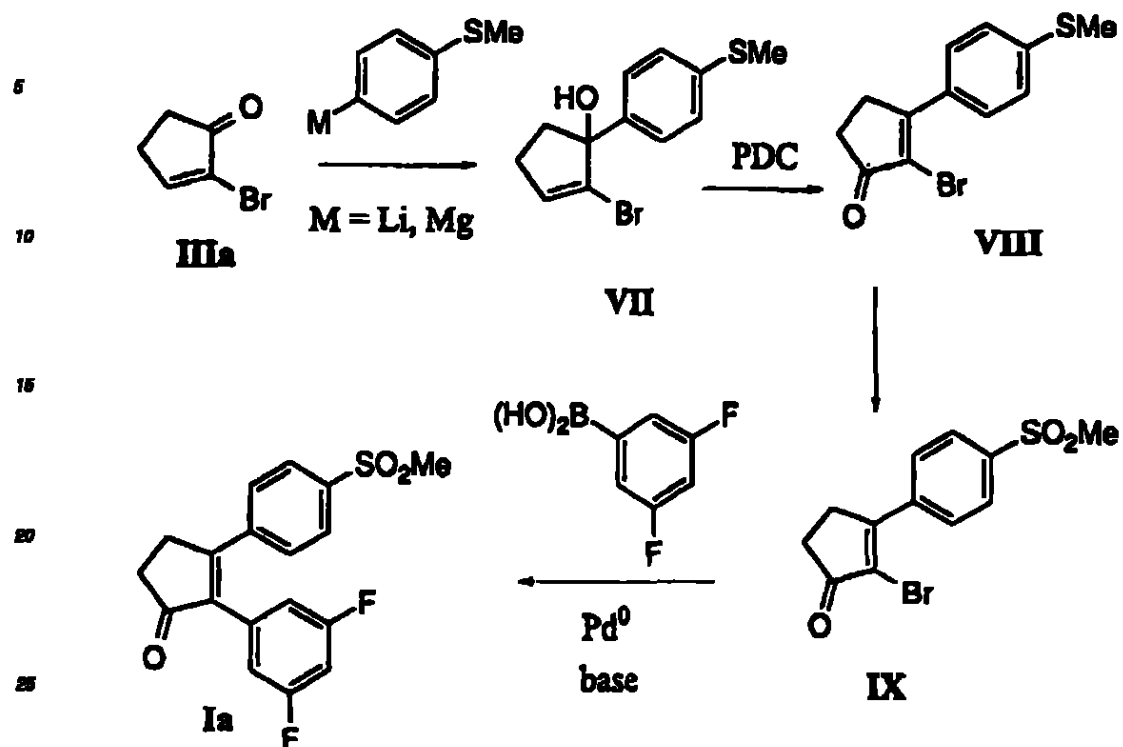
Method A

Cyclopentanone (II) may be halogenated with bromine or iodine followed by treatment with a base to give III (see Organic Syntheses 61 65). 3,5-Difluorophenylboronic acid may then be added via a palladium-catalyzed coupling reaction to form IV. 4-Bromothiobanisole may be metalated with *n*BuLi or magnesium, and then treated with IV to give the alcohol V. Oxidation with allylic transposition may then be accomplished using an oxidant such as PDC to give cyclopentanone VI. Sulfide oxidation using an oxidant such as H_2O_2 in the presence of a tungstate catalyst, MMPP, or mCPBA then provides sulfone Ia. Alternatively, VI may be converted to sulfonamide Ib as described in U.S. Patent 5,474,985, Method A.

**Method B**

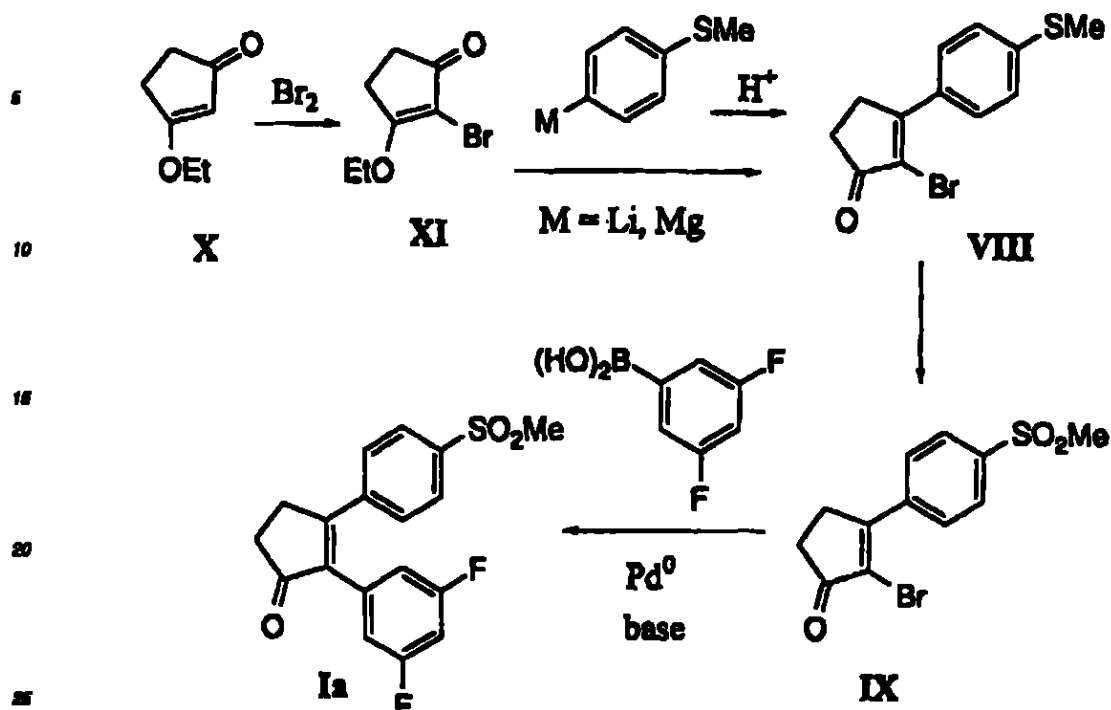
To bromocyclopentenone IIa is added lithio or magnesium thioanisole to give tertiary alcohol VII. Oxidation with a reagent such as PDC then provides the ketone VIII. The sulfide may be oxidized at this point using an oxidant such as H₂O₂ in the presence of a tungstate catalyst, NIMPP, or mCPBA to give the sulfone IX. Palladium-catalyzed coupling of 3,5-difluorophenylboronic acid then provides Ia.

47B 47D

**Method C**

3-Ethoxycyclopentanone (X) may be brominated followed by treatment with a base to give XI (see Organic Syntheses 61 65). To bromocyclopentanone XI is added lithio or magnesium thioanisole followed by acid rearrangement of the intermediate addition product to give VIII. The sulfide may be oxidized at this point using a oxidant such as H_2O_2 in the presence of a tungstate catalyst, MMPP, or mCPBA to give the sulfone IX. Palladium-catalyzed coupling of 3,5-difluorophenylboronic acid then provides Ia.

59

**EXAMPLE 1****2-(3,5-DIFLUOROPHENYL)-3-(4-(METHYLSULFONYL)PHENYL)-2-CYCLOPENTEN-1-ONE (COMPOUND A)****Step 1 3-(4-(Methylthio)phenyl)-2-cyclopenten-1-one**

To a -65°C solution of 4-bromothiobenzene (61 g, 0.3 mol) in THF (800 mL) was added a solution of *n*-BuLi (2.3 M in hexanes, 120 mL) at a rate so as to maintain an internal temperature below -55°C . The resulting slush was stirred at -65°C for 2 h, then treated with a solution of 3-ethoxy-2-cyclopenten-1-one (35 g, 0.28 mmol) in THF (50 mL). After 30 min at -65°C , the solution was warmed to 0°C and quenched with sat. aq. NH_4Cl (400 mL). The product was extracted with 3 x 1 L of EtOAc and the combined extracts were dried over MgSO_4 and concentrated. The resulting material was swished in 200 mL of 1:1 EtOAc/hexanes to provide 45 g of the title compound as a white solid.

Step 2 2-Bromo-3-(4-(methylthio)phenyl)-2-cyclopenten-1-one

To a suspension of 3-(4-(methylthio)phenyl)-2-cyclopenten-1-one (9.64 g, 47.2 mmol) in CCl_4 (200 mL) was added a solution of bromine (5 mL) in CCl_4 (80 mL) over 20 min. The resulting orange suspension was stirred for 1.5 h, then cooled in an ice-bath, and triethylamine (14 mL, 100 mmol) was added. After 30 min, the mixture was quenched with 1M HCl (300 mL) and extracted with CH_2Cl_2 . The organic phase was washed with brine, filtered through cotton and evaporated. Purification by silica gel chromatography, eluting with 90% CH_2Cl_2 /hexanes gave the title compound (7.13 g).

Step 3 2-Bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

To a 0°C solution of 2-bromo-3-(4-(methylthio)phenyl)-2-cyclopenten-1-one (5.73 g, 20.2 mmol) in CH_2Cl_2 (100 mL) and MeOH (50 mL) was added MMPP (19 g, 30.7 mmol). The mixture was stirred 5 h at r.t., then concentrated. The residue was partitioned between sat. aq. NaHCO_3 and CH_2Cl_2 . The organic phase was washed with brine, filtered through cotton and evaporated. The resulting solid was swished in CH_2Cl_2 /hexanes to provide the title compound (5.57 g).

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Step 4 2-(3,5-Difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

To a mixture of 2-bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (884 mg, 2.11 mmol), 3,5-difluorophenylboronic acid (832 mg, 5.27 mmol), tris(dibenzylideneacetone)dipalladium(0) (83 mg, 0.09 mmol), and triphenylphosphine (96 mg, 0.36 mmol) was added 40 mL of 3:1:1 toluene:n-propanol:water and the mixture was purged with nitrogen. After stirring 10 min, diethylamine (1.1 mL, 10.6 mmol) was added and the solution was heated to reflux for 4 h. The mixture was cooled and partitioned between 1M NaOH and EtOAc. The organic phase was washed with water, 1M HCl and brine, and dried over MgSO₄. Purification by silica gel chromatography, eluting with 50% CH₂Cl₂/hexanes, followed by crystallization from CH₂Cl₂/ether/hexanes gave the title compound (223 mg).

¹H NMR (CD₃COCD₃) δ 7.95 (2H, d), 7.85 (2H, d), 6.98 (1H, m), 6.82 (2H, m), 3.19 (2H, m), 3.15 (3H, s), 2.68 (2H, m).

EXAMPLE 1AStep 1 2-Bromo-2-cyclopenten-1-one

To a 0 °C solution of 2-cyclopenten-1-one (125 g, 1.52 mol) in CCl₄ (1.2 L) in a three-neck flask equipped with an overhead stirrer was added a solution of bromine (269 g, 1.68 mol) in CCl₄ (400 mL) dropwise over 4 h, maintaining an internal temperature <2 °C. A solution of Et₃N (310 mL, 2.22 mol) in CCl₄ (200 mL) was then added dropwise over 1.5 h, maintaining an internal temperature <10 °C. The resulting suspension was warmed to r.t. for 1 h, then cooled to 0 °C and filtered. The filtrate was washed with two 700 mL portions of 3M HCl and 500 mL of brine, then filtered through cotton. Concentration provided 228 g of an orange oil which was crystallized from 150 mL of 2:1 hexane: ether to provide 191 g of the title compound.

¹H NMR (CD₃COCD₃) δ 7.94 (1H, t), 2.72 (2H, m), 2.46 (2H, m).

Step 2 2-Bromo-3-(4-(methylthio)phenyl)-2-cyclopenten-1-one

To a -78 °C solution of 4-bromothiobenzonitrile (35.1 g, 173 mmol) in THF (500 mL) was added nBuLi (1.6M in hexanes, 107.5 mL, 172 mmol). The solution was stirred for 45 min, then a solution of 2-bromo-2-cyclopenten-1-one (25.4 g, 158 mmol) in THF (150 mL) was added and the mixture was allowed to warm to 0 °C and was quenched with saturated aqueous NH₄Cl. The majority of the solvent was removed *in vacuo* and the residue was suspended in water and extracted with two portions of EtOAc. The organic layers were washed with brine, dried over MgSO₄, filtered and concentrated. This material was dissolved in DMF (300 mL), cooled to 0 °C and treated with PDC (72.4 g, 192 mmol). The resulting mixture was warmed to r.t. and stirred for 2 h, then poured into water (1.2 L) and extracted with two 500 mL portions of EtOAc. The organic layers were washed with brine, dried over MgSO₄, filtered and concentrated to give the title compound as a light brown solid which was used directly in the next step.

Step 3 2-Bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

To a 0 °C solution of 2-bromo-3-(4-(thiomethyl)phenyl)-2-cyclopenten-1-one in 2:1 CH₂Cl₂/MeOH (500 mL) was added MMPP (100 g). The mixture was stirred at r.t. overnight, then concentrated and partitioned between saturated NaHCO₃, 1M Na₂S₂O₃ and CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂, and the combined organics were washed with brine, filtered through cotton and evaporated. The resulting solid was washed in CH₂Cl₂/ether to provide 23 g of the title compound.

¹H NMR (CD₃COCD₃) δ 8.12 (4H, m), 3.22 (2H, m), 3.20 (3H, s), 2.69 (2H, m).

Step 4 3,5-Difluorophenylboronic acid

To a -78 °C solution of 1-bromo-3,5-difluorobenzene (50 g, 0.26 mol) in ether (880 mL) was added nBuLi (2.4 M in hexanes, 108 mL, 0.26 mol) dropwise over 20 min. The resulting solution was stirred for 10 min, then treated with triisopropylborate (61 mL, 0.27 mol). The reaction mixture was warmed to 0 °C for 30 min, then quenched with 1 M HCl. After stirring 30 min, the mixture was partitioned between ethyl acetate and water. The organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated. The resulting product was dried under high vacuum overnight to give 38 g of the title compound.

61

¹H NMR (CD₃COCD₃) δ 7.50 (2H, br s), 7.40 (2H, m), 7.04 (1H, m),

Step 5 2-(3,5-Difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopentan-1-one

A mixture of 2-bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopentan-1-one (52.2 g, 166 mmol), 3,5-difluorophenylboronic acid (31.9 g, 202 mmol), tris(dibenzylideneacetone)dipalladium(0) (3.3 g, 3.6 mmol), and triphenylphosphine (1.89 g, 7.2 mmol) were dissolved in toluene (800 mL) and nPrOH (250 mL) and degassed. After stirring for 10 min, diethylamine (21 mL, 203 mmol) and water (250 mL) was added. The mixture degassed again, heated to reflux for 1h, then cooled and poured into EtOAc (2L). The aqueous layer was separated, and the organic layer was washed with 0.2N NaOH (500 mL), 0.5N HCl (500 mL) and brine. The organic phase was then dried over MgSO₄, filtered through celite and evaporated. The resulting light brown solid was swished in hot EtOAc (250 mL), cooled and filtered to give 45.8 g of the title compound, m.p. 174-175 °C.

¹H NMR (CD₃COCD₃) δ 7.95 (2H, m), 7.66 (2H, m), 6.98 (1H, m), 6.80 (2H, m), 3.17 (2H, m), 3.12 (3H, s), 2.68 (2H, m).

B. An alternative method of preparing 2-bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopentan-1-one (Example 1, Step 3 has been developed as follows:

Step 1 2-Bromo-3-ethoxy-2-cyclopentan-1-one

To a -15 °C solution of 3-ethoxy-2-cyclopentan-1-one (165g, 1.30 mol) in 1.6L of CHCl₃ was added a solution of bromine (219 g, 1.37 mol) in CHCl₃ (200 mL) via dropping funnel over 1.5h to give a thick yellow slurry. After 30 min additional stirring, a solution of Et₃N (210 mL, 1.5 mol) in CHCl₃ (300 mL) was added via dropping funnel over 30 min. The resulting mixture was concentrated, suspended in EtOAc and filtered through a pad of 2 cm celite over 1 cm silica gel. The filtrate was concentrated, and the resulting material recrystallized from 4:1 ether/hexanes to provide 245 g of the title compound.

¹H NMR (CD₃COCD₃) δ 4.43 (2H, q), 2.95 (2H, m), 2.47 (2H, m), 1.39 (3H, t).

Step 2 2-Bromo-3-(4-methylthio)phenyl)-2-cyclopentan-1-one

To a -78 °C solution of 4-bromothiobenzole (253 g, 1.25 mol) in THF (5 L) was added nBuLi (2.5 M in hexanes, 500 mL, 1.25 mol) over 20 min to give a thick slurry which was stirred 2h at -78 °C. A solution of 2-bromo-2-cyclopentan-1-one (242 g, 1.18 mol) in THF (1 L) was then added via cannula and the mixture was allowed to warm to -10 °C. 6N HCl (430 mL) was then added and the resulting mixture stirred 20 min. EtOAc (3L) was added and the aqueous phase was separated. The organic layer was concentrated. The residue was suspended in ether and filtered to give 287 g of the title compound.

¹H NMR (CD₃COCD₃) δ 8.12 (4H, m), 3.22 (2H, m), 3.20 (3H, s), 2.69 (2H, m).

The following example pharmaceutical formulation are illustrative of the invention:

Step 3 2-Bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopentan-1-one

To a room temperature suspension of 2-bromo-3-(4-(methylthio)phenyl)-2-cyclopentan-1-one (67.4 g, 238 mmol) in EtOAc (500 mL) and CH₂Cl₂ (100 mL) was added NaWO₄ 2H₂O (3.1 g, 9 mmol) and Aliquat 336 (12 g, 30 mmol). 10 mL of 30% H₂O₂ was added and the mixture warmed to 40°C to initiate the oxidation. 65 mL of H₂O₂ was then added dropwise over 20 min with external cooling to maintain an internal temperature of approximately 50°C. The dark reaction mixture was then maintained at 40°C for 1.5 h. The aqueous layer was separated and the organic phase was washed twice with warm water. The organic phase was then concentrated to 500 mL and the precipitate was filtered and washed with ether to give 52.2 g of the title compound as a white solid.

474
480

EXAMPLE 2

5

Wet granulated tablet composition	
Amount per tablet	Ingredient
25 mg	COX-2 inhibitor
79.7 mg	Microcrystalline cellulose
79.7 mg	Lactose monohydrate
6 mg	Hydroxypropyl cellulose
8 mg	Croscarmellose sodium
1 mg	Magnesium stearate

10

15

Tablet dose strengths of between 5 and 125 mg can be accommodated by varying total tablet weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose : lactose monohydrate. Varying amounts of up to 5 mg. of iron oxide may be added to this or the other compositions if a yellow or orange color is desired.

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EXAMPLE 2a

25

Wet granulated tablet composition	
Amount per tablet	Ingredient
125 mg	COX-2 inhibitor
425 mg	Microcrystalline cellulose
425 mg	Lactose monohydrate
10 mg	Hydroxypropyl cellulose
14 mg	Croscarmellose sodium
1 mg	Magnesium stearate

30

35

EXAMPLE 2b

40

Wet granulated tablet composition	
Amount per tablet	Ingredient
10 mg	COX-2 inhibitor
87.2 mg	Microcrystalline cellulose
87.2 mg	Lactose monohydrate
6 mg	Hydroxypropyl cellulose
8 mg	Croscarmellose sodium
1 mg	Magnesium stearate

45

50

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975
481

EXAMPLE 2c

Wet granulated tablet composition	
Amount per tablet	Ingredient
5 mg	COX-2 inhibitor
89.7 mg	Microcrystalline cellulose
89.7 mg	Lactose monohydrate
6 mg	Hydroxypropyl cellulose
8 mg	Croscarmellose sodium
1 mg	Magnesium stearate

EXAMPLE 3

Directly compressed tablet composition	
Amount per tablet	Ingredient
25 mg	COX-2 inhibitor
106.9 mg	Microcrystalline cellulose
106.9 mg	Lactose anhydrate
7.5 mg	Croscarmellose sodium
3.7 mg	Magnesium stearate

Tablet dose strengths of between 5 and 125 mg can be accommodated by varying total tablet weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose : lactose monohydrate.

EXAMPLE 3a

Directly compressed tablet composition	
Amount per tablet	Ingredient
125 mg	COX-2 inhibitor
425 mg	Microcrystalline cellulose
425 mg	Lactose anhydrate
15 mg	Croscarmellose sodium
10 mg	Magnesium stearate

482 476

EXAMPLE 3b

5

Directly compressed tablet composition	
Amount per tablet	Ingredient
10 mg	COX-2 inhibitor
42.5 mg	Microcrystalline cellulose
42.5 mg	Lactose anhydrate
4 mg	Croscarmellose sodium
1 mg	Magnesium stearate

10

15

EXAMPLE 3c

20

Directly compressed tablet composition	
Amount per tablet	Ingredient
5 mg	COX-2 inhibitor
45 mg	Microcrystalline cellulose
45 mg	Lactose anhydrate
4 mg	Croscarmellose sodium
1 mg	Magnesium stearate

25

30

EXAMPLE 4

35

Hard gelatin capsule composition	
Amount per capsule	Ingredient
25 mg	COX-2 inhibitor
37 mg	Microcrystalline cellulose
37 mg	Lactose anhydrate
1 mg	Magnesium stearate
1 capsule	Hard gelatin capsule

40

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Capsule dose strengths of between 1 and 50 mg can be accommodated by varying total fill weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose : lactose mono-hydrate.

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EXAMPLE 5

Oral solution	
Amount per 5 mL dose	Ingredient
50 mg	COX-2 inhibitor
to 5 mL with Polyethylene oxide 400	

Solution dose strengths of between 1 and 50 mg/5mL can be accommodated by varying the ratio of the two ingredients.

EXAMPLE 6

Oral suspension	
Amount per 5 mL dose	Ingredient
100 mg	COX-2 inhibitor
150 mg	Polyvinylpyrrolidone
2.5 mg	Poly oxyethylene sorbitan monolaurate
10 mg	Benzolic acid
to 5 mL with ascorbic solution (70%)	

Suspension dose strengths of between 1 and 50 mg/5ml can be accommodated by varying the ratio of the first two ingredients.

EXAMPLE 7

Intravenous infusion	
Amount per 200mL dose	Ingredient
1 mg	COX-2 inhibitor
0.2 mg	Polyethylene oxide 400
1.8 mg	Sodium chloride
to 200mL	Purified water

Claims

1. A pharmaceutical composition for the treatment of cyclooxygenase-2 mediated diseases, said composition comprising a therapeutically effective amount of a compound which is 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopentan-1-one and a pharmaceutically acceptable carrier.
2. A pharmaceutical composition comprising 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopentan-1-one and a pharmaceutically acceptable carrier.
3. A pharmaceutical composition according to Claim 1 or 2 comprising 10 to 250 mg 2-(3,5-difluorophenyl)-3-(4-

4/84 473

(methylsulfonyl)phenyl)-2-cyclopentan-1-one and a pharmaceutically acceptable carrier.

4. A composition according to Claim 1 or 2 comprising 10, 20, 30, 40 or 50 mg of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one.
5. A composition according to Claim 1 or 2 comprising 60, 70, 80, 90, 100, 110, or 120 mg of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one.
6. A composition according to Claim 1 or 2 comprising 60 to 120 mg of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one.
7. A composition according to Claim 1 or 2 comprising 10 to 50 mg of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one.
8. A method of treating an inflammatory disease susceptible to treatment with an non-steroidal anti-inflammatory agent comprising administration to a patient in need of such treatment 10 to 250 mg 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one.
9. A method according to Claim 8 comprising administration to a patient in need of such treatment 10, 20, 30, 40 or 50 mg of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one.
10. A method according to Claim 8 comprising administration to a patient in need of such treatment 60, 70, 80, 90, 100, 110, or 120 mg of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one.
11. A method according to Claim 8 comprising administration to a patient in need of such treatment 60 to 120 mg of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one.
12. A method according to Claim 8 comprising administration to a patient in need of such treatment 10 to 50 mg of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one.
13. A method according to Claim 8 for the treatment of non-chronic headache, pain or swelling.
14. A method according to Claim 8 for the treatment of osteoarthritis.
15. A method according to Claim 8 for the treatment of rheumatoid arthritis.
16. Use of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one in the manufacture of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.
17. Use according to claim 16 of 10 to 250 mg 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one in the manufacture of a dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.
18. Use according to Claim 16 of 10, 20, 30, 40 or 50 mg of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one in the manufacture of a dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.
19. Use according to Claim 16 of 60, 70, 80, 90, 100, 110, or 120 mg of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one in the manufacture of a dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.
20. Use according to Claim 16 of 10 to 50 mg of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one in the manufacture of a dosage form of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.
21. Use according to Claim 16 of 60 to 120 mg of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one in the manufacture of a dosage form of a medicament for the treatment of an inflammatory disease susceptible

67

to treatment with a non-steroidal anti-inflammatory agent.

22. Use according to Claim 16 of 10 to 50 mg of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one in the manufacture of a dosage form of a medicament for the treatment of osteoarthritis.

23. Use according to Claim 16 of 60 to 120 mg of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one in the manufacture of a dosage form of a medicament for the treatment of osteoarthritis.

24. Use according to Claim 16 of 10 to 50 of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one in the manufacture of a dosage form of a medicament for the treatment of rheumatoid arthritis.

25. Use according to Claim 16 of 60 to 120 of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one in the manufacture of a dosage form of a medicament for the treatment of rheumatoid arthritis.

26. Use according to Claim 16 of 10 to 50 mg of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one in the manufacture of a dosage form of a medicament for the treatment of non-chronic headache, pain or swelling.

27. Use according to Claim 16 of 60 to 120 mg of 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one in the manufacture of a dosage form of a medicament for the treatment of non-chronic headache, pain or swelling.

28. A compound 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one.

29. A compound 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one, for use in therapy.

30. Crystalline 2-(3,5-difluorophenyl)-3-(4-methylsulfonyl)phenyl)-2-cyclopentan-1-one.

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Doctor,
JAIRO RUBIO ESCOBAR
Superintendente de Industria y Comercio
E. S. D.

Referencia : Expediente N° 00-97644
Asunto : Remisión de información a la solicitud de patente de
Invencción titulada "COMPOSICION DE
LIBERACION DUAL DE UN INHIBIDOR DE
CICLOOXIGENASA-2".
Solicitante: PHARMACIA CORPORATION.

Yo, Luis Fernando Rincón Cuellar, abogado con tarjeta profesional N° 113438 del consejo superior de la judicatura, en mi condición de apoderado 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 por orden expresa de mi representada, con el animo de colaborar con esa Entidad en la decisión que sobre la patentabilidad de la solicitud de la referencia se tomará, me permito solicitarle, muy respetuosamente, dar curso a la siguiente información relativa al arte anterior relevante para que sea tomado en cuenta en el estudio de patentabilidad de la solicitud de patente de Invencción de la referencia.

89

1. PETICIÓN.

Ruego al Señor Superintendente, **NEGAR**, en los términos de artículo 48 de la Decisión 486 de 2000 de la CAN, la Solicitud de Patente de Invencción

487 481

denominada **"COMPOSICION DE LIBERACION DUAL DE UN INHIBIDOR DE CICLOOXIGENASA-2"**, cuyo solicitante es **PHARMACIA CORPORATION**, con base en los siguientes hechos y fundamentos de derecho, relacionados con el incumplimiento de los requisitos fundamentales exigidos para la concesión de Patentes de Invención, según la legislación vigente.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 26 de diciembre de 2000, reivindicando prioridad bajo US 60/181,604 10/02/2000; y, US 60/202,270 05/05/2000, publicado en Colombia en la Gaceta de la Propiedad Industrial N° 536, bajo NP 642., pág. 221.

2.2. La solicitud colombiana 00-97644 tiene como objeto una composición farmacéutica que comprende una o más unidades de dosis administrables oralmente, incluyendo cada una primera fracción de un fármaco inhibidor selectivo de ciclooxigenasa-2 de baja solubilidad en agua en una cantidad de alrededor de 10 mg a alrededor de 400mg, estando dicha primera fracción en solución en un solvente farmacéuticamente aceptable y/o presenta en partículas sólidas de liberación inmediata con un tamaño de partícula D90 menor que alrededor de 1 μ m; y una segunda fracción de dicho fármaco en una cantidad de alrededor de 10 mg a alrededor de 400mg, estando presente dicha segunda fracción en partículas sólidas con un tamaño de partícula D90 mayor de alrededor de 25 μ m y/o en partículas de liberación controlada, liberación lenta, liberación programada, liberación temporizada, liberación por pulsación, liberación sostenida o liberación extendida; en donde dicha primera y segunda fracción se hallan presentes en una relación de alrededor de 10:1 a alrededor 1:10 en la composición. Adicionalmente, reivindica un método

70

para tratar una condición médica o trastorno en un sujeto donde es indicado el tratamiento con un inhibidor de ciclooxigenasa-2, que comprende administrar oralmente 1 a alrededor de 4 unidades de dosis de una composición de cualquiera de las reivindicaciones 1, 17, 19 o 25 una vez al día.

2.3. Según lo expuesto, la presente solicitud pretende reivindicar un método terapéutico tal y como lo define en la cláusula 32. Según la decisión 486 de la CAN, se establece claramente en su artículo número 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 animales"*. Lo aquí reivindicado no es más que un plan de dosificación tal como un método de tratamiento. Claramente se deduce que el objeto de la presente solicitud no puede ser objeto de patente en Colombia.

2.4. Adicionalmente, el artículo 14 de 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"*. A todas luces, un plan de dosificación tal y como lo define en el capítulo reivindicatorio en su cláusula 32, no puede reproducirse a nivel industrial. Su objeto es la derivación de practicar un método terapéutico, tal como las consecuencias de su administración. La presente solicitud carece de aplicación Industrial ya que como se demostró en el apartado interior lo que se está reclamando son las características o resultados de aplicar un método de tratamiento. Éstos no son aplicables industrialmente porque primero no se obtiene un resultado mediante el empleo de materias o fuerzas de la

71

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naturaleza; y segundo no es repetible ya que usados los medios previstos no se obtiene siempre el mismo resultado. Por lo tanto el objeto de la presente invención no cumple con el requisito de la aplicación industrial.

- D1 US 5,633,272 (1997-05-27)
- D2 EP 0 863 134 A (1998-09-09)

2.5. El documento D1 afecta directamente la novedad del presente documento dado que revela con anterioridad un inhibidor de ciclooxienasa-2. Para ello verse ejemplo 1 del D1. En el documento D1 se revela que para propósitos terapéuticos, los compuestos activos de dicho documento anterior se combinan normalmente con uno o más adyuvantes apropiados para la ruta de administración indicada. Si se administran por vía oral, los compuestos pueden mezclarse con lactosa, sacarosa, polvo de almidón, ésteres celulósicos de ácidos alcanóicos, ésteres alquílicos de celulosa, talco, ácido esteárico, estearato magnésico, óxido magnésico, sales sódica y cálcica de ácidos fosfórico y sulfúrico, goma arábica, alginato sódico, polivinilpirrolidona y/o poli(alcohol vinílico), y a continuación formarse como tabletas o encapsularse para una administración cómoda. Según se revela en dicho documento anterior, tales cápsulas o tabletas pueden contener una formulación de liberación controlada que puede proporcionarse en una dispersión de compuesto activo en hidroxipropilmetilcelulosa. De igual forma se define que las formulaciones para administración parenteral pueden estar en la forma de soluciones o suspensiones para inyección, estériles, isotónicas, acuosas o no acuosas. Según dicho documento anterior D1, revela particularmente en la columna 41 línea 48 a columna 42 línea 4 que una formulación que incluye un inhibidor de ciclooxienasa-2 pueden prepararse a partir de

72

polvos o gránulos estériles que tienen uno o más de los portadores o diluyentes para usar en las formulaciones para administración oral. Igualmente se define que los compuestos pueden disolverse en agua, polietilenglicol, propilenglicol, etanol, aceite de maíz, aceite de semillas de algodón, aceite de cacahuete, aceite de sésamo, alcohol bencílico, cloruro sódico y/o diversos tampones. Así las cosas es claro que lo reivindicado en el presente documento objeto de remisión, se define varios adyuvantes y modos de administración ampliamente conocidos en la técnica farmacéutica. De hecho, en el documento anterior en su descripción se revelan varias presentaciones farmacéuticas para la administración un inhibidor de ciclooxienasa-2, tal como la cantidad de compuestos terapéuticamente activos que se administran y el régimen de dosificación para tratar un estado de enfermedad con los compuestos y/o las composiciones donde se define que dependen de una variedad de factores, incluyendo la edad, el peso, el sexo y el estado médico del sujeto, la gravedad de la enfermedad, la ruta y la frecuencia de administración y el compuesto particular empleado, y así pueden variar ampliamente. Según este documento D1 en la evaluación biológica, particularmente en la columna 41, líneas 32 a 47, define las composiciones farmacéuticas pueden contener ingredientes activos en el intervalo de aproximadamente 0,1 a 2000 mg, preferiblemente en el intervalo de aproximadamente 0,5 a 500 mg y lo más preferiblemente entre aproximadamente 1 y 100 mg similar a lo reivindicado en la cláusula 1 de la presente solicitud objeto de remisión. Según este texto anterior, se revela que puede ser apropiada una dosis diaria de aproximadamente 0,01 a 100 mg/kg de peso corporal, preferiblemente entre aproximadamente 0,5 y aproximadamente 20 mg/kg de peso corporal y lo más preferiblemente entre aproximadamente 0,1 y 10 mg/kg de peso corporal. La dosis diaria puede administrarse en de una a cuatro dosis al día. A todas luces, este documento anterior revela

73

491 485

la misma materia reivindicada en la solicitud objeto de remisión. Por lo tanto, la presente solicitud, a la luz del documento D1, carece del requisito de NOVEDAD, dado que lo que pretende se encuentra publicado antes de la radicación de la prioridad de la solicitud Colombiana.

2.6. Por su parte, el documento D2 revela un uso de un nuevo compuesto anti-inflamatorio inhibidor de ciclooxigenasa 2, como composiciones que contiene una dosis permitida de 10 a 250 mg. Este documento D2, revela la coadministración con derivados opioid según la página 3 líneas 54 a 55. En los ejemplo 2, 2a, 2b, 2c, 3, 3^a, 3b, 3c del D2 se describe comprimidos para tabletas orales que contiene 5, 10, 25 y 125 mg de un agente activo en asociación con algún excipiente preferido. Según lo expuesto en dicho documento anterior D2, en combinación con el documento D1, a todas luces, cualquier persona versada en la materia, puede deducir el plan de dosificación en 1 mg a 100 mg por dosis y uno más excipientes farmacéuticamente aceptables reivindicados en la presente solicitud. Cualquier persona versada en la materia podrá deducir lo definido en las reivindicaciones de la presente solicitud objeto de remisión, especialmente a partir de lo que dicta el documento D2 en los ejemplos, combinado con la descripción del D1 en lo concerniente al inhibidor de ciclooxigenasa 2, de manera que podrá resolver el problema planteado en la presente solicitud y llegar a la misma solución propuesta. Por lo tanto, la presente solicitud, a la luz del documento D1 en combinación con el documento D2, carece del requisito de ALTURA INVENTIVA, dado que lo que pretende es derivable del arte anterior.

74

2.7.1. **CARECE DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la*

técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”. A la fecha de prioridad, 5 de mayo de 2000, ya era conocido, pues como se demostró, era parte del arte anterior la materia sobre la cual busca protección en el capítulo reivindicatorio con base en el documento D1.

2.7.2. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”. A la fecha de prioridad, 5 de mayo de 2000, el documento D1 en combinación con D2, es posible deducir el uso y las alternativas farmacéuticas de composiciones de liberación dual de un inhibidor de ciclooxigenasa-2.*

2.7.3. 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 lo que se está reclamando es un método de tratamiento tal como un plan matemático de dosificación y las consecuencias de seguir dicho tratamiento. Éstos NO son aplicables industrialmente porque primero no se obtiene un resultado mediante el empleo de materias o fuerzas de la naturaleza; y segundo no es repetible ya que usados los

75

medios previstos no se obtiene siempre el mismo resultado. Por lo tanto el objeto de la presente invención no cumple con el requisito de la aplicación industrial.

2.8. 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 los tres requisitos de patentabilidad.

2.9. Por consiguiente, si se concede el registro solicitado se induciría al monopolio de un producto que no cumple con los requisitos primordiales exigidos por la mencionada Decisión 486.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente remisión y negar el registro Patente de invención denominada **“COMPOSICION DE LIBERACION DUAL DE UN INHIBIDOR DE CICLOOXIGENASA-2”**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 536 del 30 de enero de 2004, en la página 221, bajo el NP 642.

3. PRUEBAS.

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

494 138

- D1 US 5,633,272 (1997-05-27)
- D2 EP o 863 134 A (1998-09-09)

4. FUNDAMENTO DE DERECHO.

Fundamento esta remisión en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 48 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:

- D1 US 5,633,272 (1997-05-27)
- D2 EP o 863 134 A (1998-09-09)

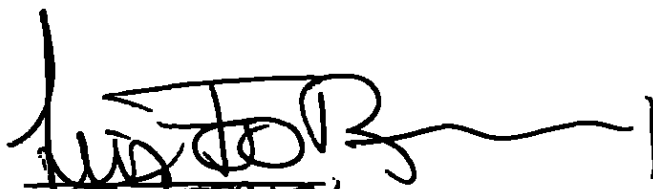
6. NOTIFICACIONES

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 de abogado situadas en la calle 119ª N° 53-99 de esta ciudad de Bogotá.

77

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Señor Superintendente,


c.c. ET 532186

78



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PODER ESPECIAL

Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
Ciudad

Referencia: Poder- Remisión de Información a la solicitud de patente N°
00-97644.

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad, identificado con la cédula de ciudadanía No 16.251.923 expedida en Palmira (Valle), domiciliado y residente en la ciudad de Barranquilla, actuando en nombre y representación de la sociedad **PROCAPS S.A.**, con NIT 890.106.527-5, manifiesto que confiero poder especial, amplio y suficiente al doctor **LUIS FERNANDO RINCÓN CUELLAR**, abogado en ejercicio, identificado con la cédula de ciudadanía número 79.532.186 de Bogotá y con tarjeta profesional número 113.438 expedida por el Consejo Superior de la Judicatura, para que adelante y lleve hasta su culminación una remisión de Información en relación a la patentabilidad de la solicitud de la referencia titulada "**COMPOSICION DE LIBERACION DUAL DE UN INHIBIDOR DE CICLOOXIGENASA-2**", cuyo solicitante es **PHARMACIA CORPORATION**.

Mi apoderado cuenta con amplias facultades para el ejercicio del presente poder, en especial las de recibir, transigir, sustituir, reasumir y deslitr.

Ante mí,


WALTER TANAKA TATEKAWA

PROCAPS S.A.

C.C. No 16.251.923 de Palmira

Acepto,


LUIS FERNANDO RINCÓN CUELLAR

C.C. 79.532.186 de Bogotá

T.P. 113.438 del C.S.J.

P
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arías

11

DILIGENCIA DE PRESENTACION PERSONAL

DECRETO 9ND DE 1970 - ART. 62

MARIA DEL S. ROMAN DE ARTETA - NIT 494 363 000 000 - BARRANQUILLA

CERTIFICADA

En B/quilla a los 20 días del mes de 05 de Mayo del 2004, comparecieron esta diligencia en su presencia: Walter Tenaoka Tenaoka

Portadores de las cédulas 16251.923

Expediente: 16251.923
Firma: [Firma]
Huellas: [Huellas]

Comparecientes

**DILIGENCIA DE RECONOCIMIENTO
Y PRESENTACION PERSONAL**

LA NOTARIA

REPUBLICA DE COLOMBIA
NOTARIA SECUNDARIA
DE BARRANQUILLA

Quien ante mí la C.C. No. 16251.923
y declaró que la firma y huella que aparecen en
el presente memorial son suyas y que el con-
tenido del mismo es cierto.
Memorial dirigido a

Sancti de Bogotá, D.C. **18 NOV 2004**

REPUBLICA DE COLOMBIA
NOTARIA DEL CIRCULO DE
BOGOTA, D.C.
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE