

RAISBECK, LARA, RODRÍGUEZ & RUEDA
MIEMBROS DE LA FIRMA
BAKER & MCKENZIE

AVENIDA 82 N° 10 - 82, Piso 8
TELÉFONO: (57-1) 6341500
BOGOTÁ, D.C. COLOMBIA
WWW.BAKERINPD.COM
OFFICE.BOGOTA@BAKERNET.COM

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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

SUPERINDUSTRIA Y COMERCIO
Radicación : 01016923 00000003 Folios: 3
Fecha (AMD): 2003-07-23 13:00:32
Trámite : 002 PATENTES 0 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Ref.: Expediente No. 01.016.923

Solicitud de Patente de Invención Titulada:

"DERIVADOS DE ETÉRES DE PIRAZOL COMO
AGENTES ANTIINFLAMATORIOS
ANALGESICOS".

Solicitante: PFIZER PRODUCTS INC.

**SOLICITUD DE EXAMEN DE FONDO SEGÚN EL ARTICULO 44 DE LA
DECISION 486, GACETA No. 527**

ALVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá, D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado sustituto, de la sociedad Pfizer Products Inc., respetuosamente me permito solicitar, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina de Naciones, que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma. Adjunto recibo por el monto de \$ 335.000 pesos para cubrir la tasa correspondiente, según la Resolución 41687 del año 2002.

Atentamente,



ALVARO CORREA ORDÓÑEZ
C.C. No. 79.143.366 de Usaquén
T.P. 20.281

Anexos: Sustitución de Poder
Recibo por \$ 335.000 pesos

**DILIGENCIA DE RECONOCIMIENTO
Y PRESENTACION PERSONAL**

Ante el Notario Once del Circulo de Santa Fe de Bogotá, compareció

Quien exhibió la C.C. No. 13246
expedida en Usaquén T.P. 10/28

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 interesada

Santa Fe de Bogotá, D.C. 23 JUL 2005

Firma del Declarante

HUELLA

Autorizó la anterior Diligencia

NOTARIO ONCE DEL CIRCULO DE SANTA FE DE BOGOTÁ DE COLOMBIA
CIRCULO DE SANTA FE DE BOGOTÁ DEL CIRCULO DE
SANTA FE DE BOGOTÁ, D.C.

MARVARRO DE BAUTISTA
NOTARIA ONCE

RAISBECK, LARA, RODRÍGUEZ & RUEDA
MIEMBROS DE LA FIRMA
BAKER & MCKENZIE

AVENIDA 82 No. 10-82, 6º Piso
TELÉFONO: (57-1) 834-1500
BOGOTÁ, D.C. COLOMBIA
WWW.BAKERNET.COM
OFFICE.BOGOTA@BAKERNET.COM

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296

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref.: Solicitud colombiana de patente No. **01.016.923**

Solicitante: **PFIZER PRODUCTS INC.**
"DERIVADOS DE ETÉRES DE PIRAZOL COMO
AGENTES ANTIINFLAMATORIOS
ANALGESICOS".

SUSTITUCIÓN DE PODER

CARLOS R. OLARTE, mayor y vecino de Bogotá. D.C., identificado como aparece al pie de mi firma, actuando en mi carácter de apoderado de la sociedad de la referencia, respetuosamente me permito manifestar que **SUSTITUYO** el poder a mi conferido por la mencionada sociedad en el doctor **ALVARO CORREA ORDÓÑEZ**, identificado con la Cédula de Ciudadanía número 79.143.366 de Usaquén y con la Tarjeta Profesional número 20.281, para que sea él quien en adelante, asuma el trámite de la presente solicitud.

El apoderado sustituto queda con las mismas facultades del principal.

Atentamente,



CARLOS R OLARTE
C.C. No. 79.782.747 de Bogotá
T. P. No. 74.295 del Consejo Superior de la Judicatura

**DILIGENCIA DE RECONOCIMIENTO
Y PRESENTACION PERSONAL**

Ante el Notario Once del ~~CIRCULO~~ de Santafé de Bogotá, compareció ~~el Sr. [illegible]~~

Quién exhibió la C.C. No. ~~[illegible]~~

expedida en ~~[illegible]~~ T.P. ~~[illegible]~~

y declaró que la firma y huella que aparecen en el presente memorial son suyas y que el contenido del mismo es cierto.

Memorial dirigido a *interesado*

Santafé de Bogotá, D.C. **5 JUL 2013**

Firma del Declarante

HUELLA

Autorizó la anterior Diligencia

NOTA: ONCE DEL CIRCULO DE SANTAFE DE BOGOTA

REPUBLICA DE COLOMBIA
NOTARIA 11 DEL CIRCULO DE
SANTAFE DE BOGOTA, D.C.

[Firma]
MONICA Z. BAUTISTA N
NOTARIA ONCE(E)

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NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO
Radicalcion : 01016923 00000003
Fecha (AMB): 2003-07-23 13:00:32
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Folios: 3

RECIBO OFICIAL DE CAJA : 03 - 43,903
FECHA : JUNIO 24 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JULIAN ANDRES VARGAS	CONSIGNACION	BANCO POPULAR	050-00110-6	13228244	24/06/2003	18,050,000.00

***** CONCEPTO *****

CANT. CONTABILISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	05 EXAMEN DE PATENTABILIDAD DE INVEN	335,000.00
	TOTAL	335,000.00

SON: TRESCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 01-16923

**EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION
FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 527, DE
FECHA 30 DE ABRIL DE 2003, EL TERMINO HABIL SEÑALADO POR LA LEY
EXPIRA EL 29 DE JULIO DE 2003.**

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO ____ **X** ____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020

Bogotá, D.C., 24 de agosto de 2008

Apoderado: Álvaro Correa Ordóñez

Oficio 000069783

REFERENCIA: Radicación No. 01-16939
Trámite 002
Evento 001
Actuación 430
Folios

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados:

- ◆Capítulo descriptivo, folios 244 a 357;
- ◆Capítulo reivindicatorio, folios 359 a 369;
- ◆1º examen de forma, folio 383;
- ◆Respuesta técnica al primer examen de forma, folios 285 y 286;
- ◆Solicitud de la cual se reivindica prioridad, folios 20 a 242;
- ◆2º examen de forma folio 293;
- ◆Solicitud del examen de patentabilidad, folios 296 y 297;

2. Objeto de la Invención:

La presente solicitud cuyo título es "DERIVADOS DE ETÉRES DE PIRAZOL COMO AGENTES ANTIINFLAMATORIOS/ANALGESICOS"

El objeto de la solicitud es los compuestos derivados de 1-fenil-pirazol, 2-(1H-pirazol-1-il)piridinio, 3-(1H-pirazol-1-il)piridina y 3-(1H-pirazol-1-il)piridazina, las composiciones que los comprenden.

El objeto de la invención se puede clasificar según la clasificación internacional como A61K31/4025, 31/402, 31/501.

Excepciones de Patentabilidad:

El artículo 20 de la Decisión 486 de la Comisión de la Comunidad Andina establece en su inciso d) que no serán patentables: *"los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*.

La reivindicación 10, reclama un método para tratamiento del cuerpo humano o animal, el cual incluye la administración de un compuesto, por lo tanto están inmersas bajo el alcance del artículo 20 de la Decisión 486.

Claridad de la solicitud:

En el artículo 30 de la decisión 486 de la Comisión de la Comunidad Andina se establece: *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*.

-La reivindicación 9 no es clara, puesto que no es congruente el encabezado con el resto del texto o parte caracterizante de la reivindicación, se encabeza como una composición y el resto del texto es una mezcla de uso con método terapéutico; lo correcto es caracterizar técnicamente dicha composición como tal, sin rellenar el texto de las reivindicaciones, con notas no técnicas que no definen ningún elemento la composición.

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión establece: *"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."*

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de

presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

No	Documento No.	Título	Fecha de Publicación
D1	WO9841625	Compositions Comprising a cyclooxygenase-2 inhibitor and a leukotriene A ₄ hydrosales inhibitor	27-dic-1996
D2	EP0418845	Pyrazole derivatives, process for preparaton thereof and pharmaceutical composition comprising the same.	27-mar-1991
D3	WO9738986	Substituted benzenesulfonamide derivatives as prodrugs of COX-2 inhibitors	23-oct-1997
D4	US5510496	Substituted pyrazolyl benzenesulfonamides	23-abr-1996

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"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."*

En cumplimiento de este artículo, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la Novedad:

El art.16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"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".*

La solicitud en estudio se refiere a derivados de los siguientes grupos: 1-fenil-pirazol, 2-(1H-pirazol-1-il)piridinio, 3-(1H-pirazol-1-il)piridina y 3-(1H-pirazol-1-il)piridazina y composiciones que los comprenden.

-D1 describe composiciones que comprenden un Inhibidor de leucotrieno A₄ hidrolasa y un compuesto de fórmula I que cuando por ejemplo se reemplaza en dicho compuesto de fórmula I, el sustituyente A por un anillo insaturado heterocíclico, R¹ es heterocíclico, cicloalquil o aril, R² es metil o amino y R³ es heterocíclico, alquilo, alquilo, alquilo, arilamino, N-aralquilamino, N-alquil-N-aralquilamino, N-alquil-N-arilamino, arilo, arilo, aralquilo, alquilsulfinil, alquilsulfonyl, arilsulfonyl; son compuestos que son reclamados como nuevos en la solicitud en estudio.

-D2 describe compuestos derivados de pirazol de fórmula (I), que al hacer por ejemplo el reemplazo de los sustituyentes, R¹ es aril sustituidos con alquilsulfonyl, R² es alquilamino, alquilo, alquilsulfinil, y R³ es heterocíclico, son compuestos que se reclaman como nuevos en la solicitud en estudio.

-D3 describe compuestos derivados de bencensulfonamidas de fórmula (I), donde por ejemplo A es un anillo heterocíclico insaturado sustituido por alquil, aril, cicloalquil-alquilo, heterocíclico; son compuestos que caen dentro de lo que se reclama como nuevo en la solicitud en estudio.

Evaluación del Nivel Inventivo:

El art. 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"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."*

-D4-describe compuestos fenil-pirazolderivados de fórmula (I), la única diferencia con la solicitud en estudio es que en D4 el R³, no es hidrogeno pero conserva las mismas propiedades farmacológicas que la solicitud en estudio, tal como puede verse la anterioridad anticipa a describir la materia genéricamente que se reclama como con actividad inventiva en la presente solicitud.

Considerando la actividad inventiva, vemos que la solicitud en estudio basa su nivel inventivo compuestos derivados de los grupos 1-fenil-pirazol, 2-(1H-pirazol-1-

II) piridinio, 3-(1H-pirazol-1-il)piridina y 3-(1H-pirazol-1-il)piridazina, o sea, lo que se observa es una generalización de la anterioridad, por lo tanto se considera que la solicitud en estudio no posee el proceso creativo, para obtener resultados inesperados, que no se deduzcan del estado de la técnica en forma evidente, para un técnico con conocimientos medios en la materia, porque la anterioridad comprende las características esenciales de la invención en estudio, que los derivados del mismo tipo aril-pirazoles, tengan las mismas aplicaciones como agentes antiinflamatorios analgésicos.

Además después de revisado el estado de la técnica vemos que la solicitud en estudio no posee unidad inventiva a posteriori, porque posee los siguientes grupos de invenciones 1-fenil-pirazol, 2-(1H-pirazol-1-il)piridinio, 3-(1H-pirazol-1-il)piridina y 3-(1H-pirazol-1-il)piridazina, ya que no aparece que un elemento estructural significativo especial y compartido, para todas las alternativas que se reclaman, esa estructura significativa debe ser la característica técnica especial, o sea, no debe ser una estructura conocida y claramente definida. La estructura (I) que aparece como característica especial en la solicitud, es una estructura conocida y no puede ser considerada que define una nueva contribución al estado de la técnica, por lo tanto no se puede constituir en la característica especial de la invención.

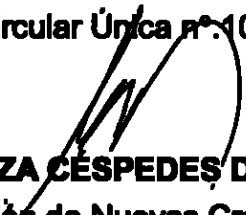
Tal como se puede ver los compuestos reclamados en la solicitud en estudio, mirados contra los compuestos de las anterioridades se ven como una selección de los de la solicitud en estudio, o sea, las anterioridades son más específicas que la solicitud en estudio.

No.	Documento	Reivindicaciones Afectadas	Requisito que afecta
D1	WO9641625	1 a 10	Novedad y nivel inventivo
D2	EP0418845	1 a 10	Novedad y nivel inventivo
D3	WO9738986	1 a 10	Novedad y nivel inventivo
D4	US5510496	1 a 10	Nivel inventivo

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En cumplimiento del artículo 45 de la decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5° del título 1° de la Circular Única n° 10 de 2001.


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

El anterior requerimiento fue notificado por fijación en lista de fecha 31 AGO 2006

CONCEPTO TÉCNICO No. <u>1379</u>	EXAMINADOR TÉCNICO Código: 202012
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D1

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PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/00, 31/10, 31/18, 31/13, 31/135, 31/19, 31/34, 31/435, 31/163, 31/215, 31/38, 31/46		A1	(11) International Publication Number: WO 96/41625 (43) International Publication Date: 27 December 1996 (27.12.96)
(21) International Application Number: PCT/US96/10105 (22) International Filing Date: 11 June 1996 (11.06.96) (30) Priority Data: 08/489,468 12 June 1995 (12.06.95) US (71) Applicant: G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors: ISAKSON, Peter, C.; 2292 Ridgely Woods Drive, Clarkson Valley, MO 63005 (US). ANDERSON, Gary, D.; 1886 Woodhollow Drive #203, Maryland Heights, MO 63043 (US). GREGORY, Susan, A.; 4400 Lindell Boulevard #20A, St. Louis, MO 63108 (US). (74) Agents: BULOCK, Joseph, W. et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).			(51) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GR, HU, IL, IS, JP, KR, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BI, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: COMPOSITIONS COMPRISING A CYCLOOXYGENASE-2 INHIBITOR AND A LEUKOTRIENE A₄ HYDROLASE INHIBITOR (57) Abstract Combinations of a cyclooxygenase-2 inhibitor and a leukotriene A ₄ hydrolase inhibitor are described for treatment of inflammation and inflammation-related disorders.			

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**COMPOSITIONS COMPRISING A CYCLOOXYGENASE-2- INHIBITOR AND A LEUKOTRIENE-A₄-
HYDROLASE-INHIBITOR**

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FIELD OF THE INVENTION

This invention is in the field of antiinflammatory pharmaceutical agents and specifically relates to co-
10 administration of an inhibitor of cyclooxygenase-2 and a leukotriene A₄ hydrolase inhibitor for treating inflammation and inflammation-related disorders, such as arthritis.

15

BACKGROUND OF THE INVENTION

Prostaglandins play a major role in the inflammation process, and the inhibition of prostaglandin production, especially production of
20 PGG₂, PGE₂ 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
25 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
30 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
35 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
5 effects.

In another portion of the arachidonic acid
pathway, physiologically active leukotrienes, such as
leukotriene B₄ (LTB₄), leukotriene C₄ (LTC₄) and
leukotriene D₄ (LTD₄) and other metabolites, are
10 produced by the 5-lipoxygenase-mediated (5-LO)
oxidation of arachidonic acid. These leukotrienes have
been implicated in various inflammation-related
disorders and allergic diseases, and thus compounds
which inhibit leukotriene A₄ conversion to leukotriene
15 B₄, such as compounds which inhibit leukotriene A₄
hydrolase are useful in the treatment of disease states
in which leukotrienes play an important role.

It is believed that selective inhibitors of
cyclooxygenase-2 and of leukotriene A₄ hydrolase, which
20 affect the two enzymes at low concentrations, will
decrease the incidence and severity more completely.
These compositions also will beneficially affect the
damage caused by the various inflammatory diseases and
inflammation-related disorders mediated by
25 cyclooxygenase-2 and leukotriene A₄ hydrolase. These
compositions also will not have the level of
gastrointestinal side effects commonly associated with
traditional NSAIDs.

Compounds which selectively inhibit
30 cyclooxygenase-2 have been described in U.S. patents
5,380,738, 5,344,991, 5,393,790, 5,466,823, 5,434,178,
5,474,995, 5, 510,368 and WO documents WO96/06840,
WO96/03388, WO96/03387, WO95/15316, WO94/15932,
WO94/27980, WO95/00501, WO94/13635, WO94/20480, and
35 WO94/26731.

Compounds which inhibit leukotriene A₄ hydrolase
have been described in WO96/11192 and WO96/10999.

Combined therapies of NSAIDs and other reagents are known in the art. Brooks and Karl describe the treatment of hay fever with combined antihistamines and a cyclooxygenase-inhibiting drug (flurbiprofen) (J. Allergy Clin. Immunol., 81, 110 (1988)). J. Basmajian (Spine, 14, 438 (1989)) describes the combination of the analgesic diflunisal and an antispasm agent in the treatment of back pain. V. Fossaluzza and S. DeVita describe the combined therapy of ibuprofen and an antispasm agent to reduce morning stiffness associated with primary fibromyalgia syndrome (Int. J. Clin. Pharm. Res., XII, 99 (1992)). R. Greenwald et al. (J. Rheumatol., 19, 927 (1992)) report the combination of tetracycline and the NSAID flurbiprofen ameliorates the tissue damage associated with rheumatoid arthritis.

Combination analgesics have been reported (W. Beaver, Am. J. Med., 77, 38 (1984)) although such combinations do not substantially reduce adverse effects.

The combination of NSAIDs and steroids have been described. A combination of indomethacin, steroid and lipopolysaccharide has been reported for the treatment of spinal injury (L. Guth et al., Proc. Natl. Acad. Sci. USA, 91, 12308 (1994)). G. Hughes et al. describe combinations of corticosteroids with NSAIDs for the treatment of sunburn (Dermatology, 184, 54 (1992)). C. Stewart et al. (Clin. Pharmacol. Ther., 47, 540 (1990)) describe the combination of naproxen and methotrexate as safe, although concurrent administrations of methotrexate with other NSAIDs have been reported to be toxic and sometimes fatal. A combination of a dual 5-lipoxygenase/cyclooxygenase inhibitor with a glucocorticoid is described for the treatment of skin disorders (K. Tramposch, Inflammation, 17, 531 (1993)). Combinations of NSAIDs and steroids should be used in the treatment of scleritis only if patients are not responsive to any

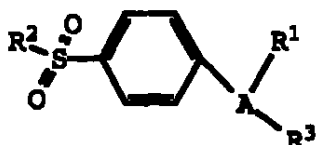
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What is claimed is :

1. A combination comprising a therapeutically-effective amount of a cyclooxygenase-2 inhibitor and a
5 leukotriene A₄ hydrolase inhibitor.

2. A combination comprising a therapeutically-effective amount of a leukotriene A₄ hydrolase inhibitor and a cyclooxygenase-2 inhibitor selected from Taisho
10 NS-398, meloxicam, floculide, Merck MK-966, Merck L-752,860 and compounds of Formula I



I

15 wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

wherein R¹ is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl,

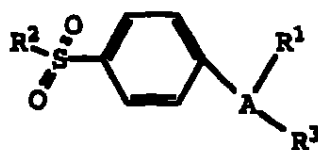
20 wherein R¹ is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and
25 alkylthio;

wherein R² is methyl or amino; and

wherein R³ is a radical selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycliloxy, alkylloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl,
30 aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl,

aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-
 5 arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl,
 10 alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl; or a pharmaceutically-acceptable salt thereof.

15 11. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising co-administering to the subject having or susceptible to such inflammation or inflammation-associated disorder, a therapeutically-effective amount
 20 of a leukotriene A₄ hydrolase inhibitor and a cyclooxygenase-2 inhibitor selected from Taisho NS-398, meloxicam, floculide, Merck MK-966, Merck L-752,860 and compounds of Formula I



I

25

wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

30 wherein R¹ is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R¹ is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl,
 35 hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino,

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15. The method of Claim 14 wherein the leukotriene A₄ hydrolase inhibitor is selected compounds of Claim 6, or a pharmaceutically-acceptable salt thereof.

5 16. The method of Claim 11 wherein the cyclooxygenase-2 inhibitor is selected compounds of Claim 7, or a pharmaceutically-acceptable salt thereof.

10 17. The method of Claim 16 wherein the cyclooxygenase-2 inhibitor is selected compounds of Claim 8, or a pharmaceutically-acceptable salt thereof.

15 18. The method of Claim 17 wherein the cyclooxygenase-2 inhibitor is selected compounds of Claim 9, or a pharmaceutically-acceptable salt thereof.

19. The method of Claim 11 wherein the condition is inflammation.

20 20. The method of Claim 11 wherein the condition is an inflammation-associated disorder.

25 21. The method of Claim 20 wherein the inflammation-associated disorder is arthritis.

22. The method of Claim 11 wherein the subject is susceptible to inflammation.

30 23. The method of Claim 11 wherein the subject is susceptible to an inflammation-associated disorder.

24. The method of Claim 23 wherein the subject is susceptible to arthritis.

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(71) Applicant: FUJISAWA PHARMACEUTICAL CO.,
LTD.
4-7, Doshomachi 3-chome Chuo-ku
Osaka-shi Osaka 541(JP)

(72) Inventor: Matsuo, Masaaki
4-12, Nakasakurazuka 5-chome

Toyonaka-shi, Osaka 560(JP)

Inventor: Tsuji, Kiyoshi

170, Hatacho

Kishiwada-shi, Osaka 596(JP)

Inventor: Konishi, Nobuhiro

22-7 Aotani

Nagasaki-shi, Kyoto 617(JP)

Inventor: Nakamura, Katsuya

22-20-306, Minagayama 2-chome,

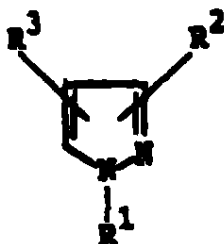
Higashinada-ku

Kobe-shi, Hyogo 658(JP)

(74) Representative: Türk, Gille, Hrabal
Brucknerstrasse 20
W-4000 Düsseldorf 13(DE)

(52) Pyrazole derivatives, processes for preparation thereof and pharmaceutical composition comprising the same.

(57) A compound of the formula :



[I]

EP 0 418 845 A1

wherein R¹ is aryl which may be substituted with substituent(s) selected from the group consisting of lower alkyl, halogen, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, hydroxy, lower alkylsulfonyloxy, nitro, amino, lower alkylamino, acylamino and lower alkyl(acyl)amino; or a heterocyclic group;

R² is hydrogen; methyl substituted with amino, lower alkylamino, halogen or alkoxy; acyl; acylamino; cyano; halogen; lower alkylthio; lower alkylsulfinyl; or a heterocyclic group; and

R³ is aryl substituted with lower alkyl, lower alkylthio, lower alkylsulfinyl, halogen, amino, lower alkylamino, acylamino, lower alkyl(acyl)amino, lower alkoxy, cyano, hydroxy or acyl; or a heterocyclic group which may be substituted with lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl;

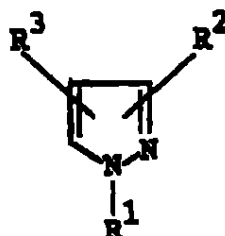
with certain provisions, pharmaceutically acceptable salts thereof, processes for their preparation and pharmaceutical compositions comprising them as an active ingredient.

Example 80

A solution of acetyl chloride (0.48 g) in ethyl acetate (10 ml) was added dropwise to an ice-cooled solution of 1-(4-fluorophenyl)-5-[4-(methylthio)phenyl]pyrazol-3-ylmethylamine (1.8 g) and triethylamine (1 g) in ethyl acetate (50 ml). The mixture was stirred at 5°C for 1 hour, washed successively with dilute hydrochloric acid, a solution of sodium bicarbonate and water, dried, and concentrated in vacuo. A mixture of the above residue (2.5 g) containing N-[1-(4-fluorophenyl)-5-[4-(methylthio)phenyl]pyrazol-3-ylmethyl]acetamide and m-chloroperbenzoic acid (2.8 g) in dichloromethane (50 ml) was stirred at room temperature overnight. The mixture was washed with a solution of sodium bicarbonate and concentrated in vacuo. To the residual powder (2.1 g) containing N-[1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazol-3-ylmethyl]acetamide was added ethanol (40 ml) and conc. hydrochloric acid (15 ml). The mixture was refluxed for 7 hours and concentrated to dryness. The residue was dissolved in water, then the solution was made basic with sodium hydroxide and extracted with ethyl acetate. The extract was washed with water, dried, and concentrated in vacuo. The obtained residue (1.4 g) was purified by column chromatography on silica gel (100 g) eluting with a mixture of chloroform and methanol (10:1) to give crystals of 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazol-3-ylmethylamine (1.0 g).
mp : 150-152°C
IR (Nujol) : 3380, 3300, 1600, 1510 cm⁻¹
NMR (CDCl₃, δ) : 1.85 (2H, s), 3.07 (3H, s), 3.88 (2H, s), 6.57 (1H, s), 7.0-7.5 (8H, m), 7.87 (2H, d, J=8Hz)
Mass (m/z) : 345 (M⁺)

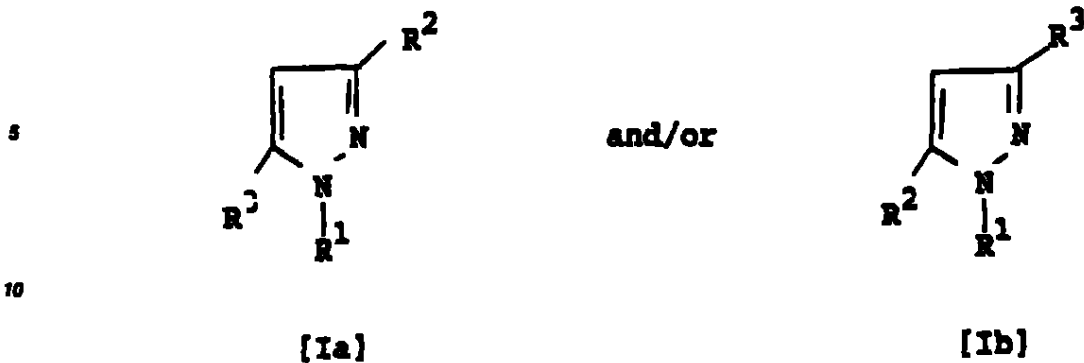
Claims

1. A compound of the formula :



[I]

wherein R¹ is aryl which may be substituted with substituent(s) selected from the group consisting of lower alkyl, halogen, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, hydroxy, lower alkylsulfonyloxy, nitro, amino, lower alkylamino, acylamino and lower alkyl(acyl)amino; or a heterocyclic group;
R² is hydrogen; methyl substituted with amino, lower alkylamino, halogen or acyloxy; acyl; acylamino; cyano; halogen; lower alkylthio; lower alkylsulfinyl; or a heterocyclic group; and
R³ is aryl substituted with lower alkyl, lower alkylthio, lower alkylsulfinyl, halogen, amino, lower alkylamino, acylamino, lower alkyl(acyl)amino, lower alkoxy, cyano, hydroxy or acyl; or a heterocyclic group which may be substituted with lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl;
provided that
when R² is carboxy, esterified carboxy or tri(halo)methyl,
then R³ is aryl substituted with lower alkylthio, lower alkylsulfinyl, amino, lower alkylamino, acylamino, lower alkyl(acyl)amino, hydroxy or acyl; or a heterocyclic group substituted with lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl; or
R¹ is aryl substituted with substituent(s) selected from the group consisting of lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, hydroxy, lower alkylsulfonyloxy, nitro, amino, lower alkylamino, acylamino and lower alkyl(acyl)amino; or a heterocyclic group;
and a pharmaceutically acceptable salt thereof.
2. A compound according to claim 1,
wherein R² is hydrogen; methyl substituted with amino, lower alkylamino or acyloxy; carbamoyl optionally substituted with substituent(s) selected from the group consisting of lower alkyl, cyclo(lower)alkyl, aryl and hydroxy; lower alkanoyl optionally substituted with lower alkoxy; a heterocycliccarbonyl; acylamino; cyano; halogen; lower alkylthio; lower alkylsulfinyl; lower alkylsulfonyl; or a heterocyclic group.
3. A compound according to claim 2,



- 15 or its salt, in the above formulas,
R⁶ is lower alkylthio, and
R¹, R² and R³ are each as defined above.
9. A pharmaceutical composition comprising a compound of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially nontoxic carrier or excipient.
- 20 10. A compound of claim 1 for use as a medicament.
11. Use of a compound of claim 1 or its pharmaceutically acceptable salt for the manufacture of a medicament for therapeutic treatment of inflammatory conditions, various pains, collagen diseases, autoimmune diseases or various immunity diseases.

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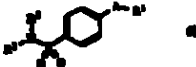
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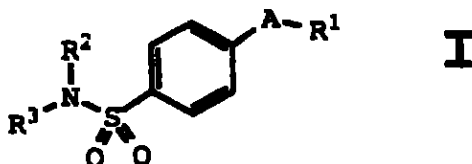
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 261/08, 233/54, 401/04, A61K 31/42, 31/415, C07D 231/12, 495/04, 263/32, C07C 311/39, C07D 207/32, 307/58 // (C07D 495/04, 335:00, 231:00)	A1	(11) International Publication Number: WO 97/38986 (43) International Publication Date: 23 October 1997 (23.10.97)
(21) International Application Number: PCT/US97/05497 (22) International Filing Date: 11 April 1997 (11.04.97) (30) Priority Data: 08/631,514 12 April 1996 (12.04.96) US (60) Parent Application or Grant (63) Related by Continuation US 08/631,514 (CIP) Filed on 12 April 1996 (12.04.96) (71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): TALLEY, John, J. [US/US]; 8772 Pine Avenue, Brentwood, MO 63144 (US). MALECHA, James, W. [US/US]; 1121 Tracy Lane, Libertyville, IL 60048 (US). BERTENSHAW, Stephen [US/US]; 8758 Pine Avenue, Brentwood, MO 63144 (US). GRANETO, Matthew, J. [US/US]; 1510 Voltaire	(74) Agents: WILLIAMS, Roger, A. et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GR, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU. ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: SUBSTITUTED BENZENESULFONAMIDE DERIVATIVES AS PRODRUGS OF COX-2 INHIBITORS		
		
(57) Abstract Prodrugs of COX-2 inhibitors of formula (I) are described as being useful in treating inflammation and inflammation-related disorders wherein A is a ring substituent selected from partially unsaturated heterocyclyl, heterocaryl, cycloalkenyl and aryl, wherein A is optionally substituted at a substitutable position with one or more radicals selected from alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, nitro, carboxyl, alkoxy, aminocarbonyl, alkoxy carbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, haloalkylsulfonyloxy, alkoxyalkylsulfonyloxy, carboxyalkoxyalkyl, cycloalkylalkyl, alkenyl, alkynyl, heterocyclyloxy, alkylthio, cycloalkyl, aryl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, alkylthioalkyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, arylalkoxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxy carbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, alkylamino, N-arylmino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonylalkyl, N-arylaminocarbonylalkyl, N-aralkylaminocarbonylalkyl, N-alkyl-N-aralkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, aralkoxy, aralkoxy, arylthio, aralkylthio, alkylsulfonyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, and N-alkyl-N-arylaminosulfonyl; wherein R¹ is selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R² is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxy carbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfonyl, halo, alkoxy and alkylthio; wherein R³ is selected from hydrido and alkoxy carbonylalkyl; and wherein R⁴ is selected from alkyl, carboxyalkyl, acyl, alkoxy carbonyl, heterocarylcarbonyl, alkoxy carbonylalkylcarbonyl, alkoxy carbonylalkylcarbonyl, amino acid residue, and alkylcarbonylaminocarbonyl; provided A is not tetrazolium, or pyridinium; and further provided A is not indanone when R³ is alkyl or carboxyalkyl; or a pharmaceutically-acceptable salt thereof.		

What is claimed is:

1. A compound of Formula I



wherein A is a ring substituent selected from partially unsaturated heterocyclyl, heteroaryl, cycloalkenyl and aryl, wherein A is optionally substituted at a substitutable position with one or more radicals selected from alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, nitro, carboxyl, alkoxy, aminocarbonyl, alkoxycarbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, haloalkylsulfonyloxy, alkoxyalkyloxyalkyl, carboxyalkoxyalkyl, cycloalkylalkyl, alkenyl, alkynyl, heterocyclyloxy, alkylthio, cycloalkyl, aryl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, alkylthioalkyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminoalkyl, N-alkyl-N-arylaminoalkyl, alkylaminocarbonylalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminoalkyl, arylsulfonyl, and N-alkyl-N-arylaminoalkyl;

wherein R¹ is selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R¹ is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl,

cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

5 wherein R² is selected from hydrido and alkoxycarbonylalkyl; and

 wherein R³ is selected from alkyl, carboxyalkyl, acyl, alkoxycarbonyl, heteroarylcarbonyl, alkoxycarbonylalkylcarbonyl, alkoxycarbonylcarbonyl, 10 amino acid residue, and alkylcarbonylaminoalkylcarbonyl;

 provided A is not tetrazolium, or pyridinium; and further provided A is not indanone when R³ is alkyl or carboxyalkyl;

15 or a pharmaceutically-acceptable salt thereof.

2. Compound of Claim 1 wherein A is selected from partially unsaturated heterocyclyl, 5- or 6-membered heteroaryl, lower cycloalkenyl and phenyl, wherein A is 20 optionally substituted at a substitutable position with one or more radicals selected from formyl, lower alkylcarbonyl, halo, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, lower 25 hydroxyalkyl, lower haloalkylsulfonyloxy, lower alkoxyalkyloxyalkyl, lower carboxyalkoxyalkyl, lower cycloalkylalkyl, lower alkenyl, lower alkynyl, heterocycliloxy, lower alkylthio, lower cycloalkyl, phenyl, 5-6 membered heterocyclyl, lower cycloalkenyl, lower 30 phenylalkyl, 5-6 membered heterocyclylalkyl, lower alkylthioalkyl, phenylcarbonyl, lower phenylalkylcarbonyl, lower phenylalkenyl, lower alkoxyalkyl, lower phenylthioalkyl, lower phenyloxyalkyl, lower phenylalkylthioalkyl, lower phenylalkoxyalkyl, lower 35 alkoxycarbonylalkyl, lower aminocarbonylalkyl, lower alkylaminocarbonyl, N-phenylaminocarbonyl, lower N-alkyl-N-phenylaminocarbonyl, lower alkylaminocarbonylalkyl, lower

- N-[[4-(3-(3-fluorophenyl)-5-methylisoxazol-4-yl)phenyl]sulfonyl]acetamide, sodium salt;
2-methyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide, sodium salt;
5 N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide, sodium salt;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]benzamide, sodium salt;
2,2-dimethyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide, sodium salt;
10 N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]butanamide, sodium salt;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]pentanamide, sodium salt;
15 N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]hexanamide, sodium salt;
N-[[4-(2-methyl-4-phenyloxazol-5-yl)phenyl]sulfonyl]acetamide, sodium salt;
N-[[4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide, sodium salt;
20 N-[[4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl)phenyl]sulfonyl]butanamide, sodium salt;
N-[[4-(5-hydroxymethyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide, sodium salt;
25 N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]glycine, sodium salt; and
N-[[4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide, sodium salt.
- 30 58. The method of Claim 39 wherein the condition is inflammation.
59. The method of Claim 39 wherein the condition is an inflammation-associated disorder.
- 35 60. The method of Claim 59 wherein the inflammation-associated disorder is pain.

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US005510496A

United States Patent [19]

Talley et al.

[11] Patent Number: 5,510,496

[45] Date of Patent: Apr. 23, 1996

[54] SUBSTITUTED PYRAZOLYL
BENZENESULFONAMIDES

[75] Inventors: John J. Talley, St. Louis, Mo.; Thomas D. Penning, Elmhurst, Ill.; Paul W. Collins, Deerfield, Ill.; James W. Malacha, Libertyville, Ill.; Stephan R. Bertenshaw, Brentwood; Matthew J. Grunata, St. Louis, both of Mo.

[73] Assignee: G.D. Searle & Co., Chicago, Ill.

[21] Appl. No.: 456,441

[22] Filed: Jun. 1, 1995

Related U.S. Application Data

[62] Division of Ser. No. 160,594, Nov. 30, 1993, Pat. No. 5,466,823.

[51] Int. Cl.⁶ _____ C07D 231/12

[52] U.S. Cl. _____ 548/365.7; 548/370.1;
548/370.4; 548/371.7; 548/372.1; 548/375.1;
548/376.1; 548/374.1; 548/377.1

[58] Field of Search _____ 548/377.1, 365.7;
514/406

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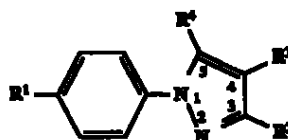
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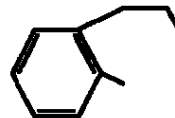
Primary Examiner—Robert W. Ramsauer
Attorney, Agent, or Firm—Joseph W. Bullock, J. Timothy Keane

[57] ABSTRACT

A class of pyrazolyl benzenesulfonamide compounds is described for use in treating inflammation and inflammation-related disorders. Compounds of particular interest are defined by Formula I:



wherein R¹ is selected from sulfamyl, fluoro, chloro, methyl, hydroxyl, methoxy and trifluoromethyl; wherein R² is selected from hydrido, difluoromethyl, trifluoromethyl, amido, dichloromethyl, trichloromethyl, pentafluoroethyl, cyano, heptafluoropropyl, difluorochloromethyl, methoxycarbonyl, dichlorodifluoromethyl, N-phenylamido, N-3-fluorophenyl amido, 2-pyridylamido, N-(4-methylphenyl)amido, hydroxypropyl, N-(3-chlorophenyl)amido, N-(4-methoxyphenyl)amido, hydroxymethyl, hydroxyethyl, carboxypropyl, carboxymethyl and carboxyethyl; wherein R³ is selected from hydrido, methyl, trifluoromethyl, fluoro, chloro and bromo; wherein R⁴ is selected from phenyl, biphenyl, pyrazinyl, cyclohexyl, cyclohexenyl and thienyl; and wherein R⁴ is optionally substituted at a substitutable position with one or more radicals selected from chloro, bromo, fluoro, methylthio, methylsulfonyl, morpholinyl, amino, methyl, ethyl, propyl, isopropyl, butyl, ethoxy, nitro, chloromethyl, trifluoromethoxy, trifluoroethoxy, fluoromethyl, methoxy, difluoromethyl, trifluoromethyl, dichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorodifluoromethyl, difluoroethyl, - and difluoropropyl; or wherein R³ and R⁴ together form



provided R³ and R⁴ are not both hydrido; or a pharmaceutically-acceptable salt thereof.

8 Claims, No Drawings

SUBSTITUTED PYRAZOLYL BENZENESULFONAMIDES

This is a divisional of U.S. application Ser. No. 08/160,594, filed Nov. 30, 1993 now U.S. Pat. No. 5,466,823.

FIELD OF THE INVENTION

This invention is in the field of anti-inflammatory 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 anti-inflammatory drug discovery. However, common non-steroidal anti-inflammatory 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.

Pyrazoles have been described for use in the treatment of inflammation. U.S. Pat. No. 5,134,142 to Matsuo et al describes 1,5-diaryl pyrazoles, and specifically, 1-(4-fluorophenyl)-5-[40(methylsulfonyl)phenyl]-3-trifluoromethyl pyrazole, as having anti-inflammatory activity.

However pyrazolyl-benzenesulfonamides have not been described as having such activity. Certain substituted pyrazolyl-benzenesulfonamides have been described in the literature as synthetic intermediates. Specifically, 4-[5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl]benzenesulfonamide has been prepared from a pyrazoline compound as an intermediate for compounds having hypoglycemic activity [R. Soliman et al, *J. Pharm. Sci.*, 76, 626 (1987)]. 4-[5-[2-(4-bromophenyl)-2H-1,2,3-triazol-4-yl]-3-methyl-1H-pyrazol-1-yl]benzenesulfonamide has been prepared from a pyrazoline compound and described as potentially having hypoglycemic activity [H. Mokhtar, *Pak. J. Sci. Ind. Res.*, 31, 762 (1988)]. Similarly, 4-[4-bromo-5-[2-(4-chlorophenyl)-2H-1,2,3-triazol-4-yl]-3-methyl-1H-pyrazol-1-yl]benzenesulfonamide has been prepared [H. Mokhtar et al, *Pak. J. Sci. Ind. Res.* 34, 9 (1991)].

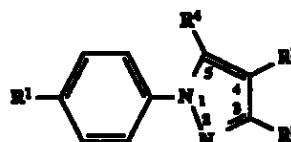
The phytotoxicity of pyrazole derivatives is described [M. Cocco et al, *Il. Farmaco-Ed. Sci.*, 40, 272 (1985)], specifically for 1-(4-(aminosulfonyl)phenyl)-5-phenyl-1H-pyrazole-3,4-dicarboxylic acid.

The use of 4-[3,4,5-trisubstituted-pyrazol-1-yl]benzenesulfonamides as intermediates for sulfonylurea anti-diabetes agents is described, and specifically, 1-[4-(aminosulfonyl)phenyl]-3-methyl-5-phenyl-1H-pyrazole-4-carboxylic acid [R. Soliman et al, *J. Pharm. Sci.*, 72, 1004 (1983)]. A series of 4-[3-substitutedmethyl-5-phenyl-1H-pyrazol-1-yl] benzenesulfonamides has been prepared as intermediates for anti-diabetes agents, and more specifically, 4-[3-methyl-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide [H. Feid-Alah, *Pharmazie*, 36, 754 (1981)]. In addition, 1-(4-[aminosulfonyl]phenyl)-5-phenylpyrazole-3-carboxylic acid has been prepared from the above described 4-[3-methyl-5-

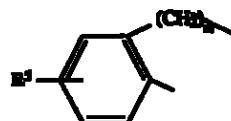
phenyl-1H-pyrazol-1-yl]benzenesulfonamide compound [R. Soliman et al, *J. Pharm. Sci.*, 70, 602 (1981)].

DESCRIPTION OF THE INVENTION

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



wherein R¹ is selected from sulfonyl, halo, alkyl, alkoxy, hydroxyl and haloalkyl; wherein R² is selected from hydrido, halo, haloalkyl, cyano, nitro, formyl, carboxyl, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, amido, alkoxy, amidoalkyl, N-monoalkylamido, N-monocarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfonyl, alkylsulfonyl, N-alkylsulfonyl, N-arylsulfonyl, arylsulfonyl, N,N-dialkylsulfonyl, N-alkyl-N-arylsulfonyl and heterocyclic; wherein R³ is selected from hydrido, halo, haloalkyl, cyano, nitro, formyl, carboxyl, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, amido, alkoxy, amidoalkyl, N-monoalkylamido, N-monocarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfonyl, alkylsulfonyl, N-alkylsulfonyl, N-arylsulfonyl, arylsulfonyl, N,N-dialkylsulfonyl, N-alkyl-N-arylsulfonyl, heterocyclic, heterocycloalkyl and aralkyl; wherein R⁴ is selected from aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R⁵ is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfonyl, alkyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, amido, N-monoalkylamido, N-monocarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, sulfonyl, N-alkylsulfonyl, amino, N-alkylamino, N,N-dialkylamino, heterocyclic, nitro and acylamino; or wherein R³ and R⁴ together form



and m is 1 to 3, inclusive; and wherein R⁵ is one or more radicals selected from halo, alkylthio, alkylsulfonyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, amido, N-monoalkylamido, N-monocarylamido, alkyl, N,N-dialkylamido, N-alkyl-N-arylamido, haloalkyl, hydrido, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, sulfonyl, N-alkylsulfonyl, amino, alkylamino, heterocyclic, nitro and acylamino; provided R² and R³ are not identical radicals selected from hydrido, carboxyl and ethoxycarbonyl; further provided that R² cannot be carboxyl when R³ is hydrido and when R⁴ is phenyl; and further provided that R⁴ is sulfonyl or N-alkylsulfonyl when R¹ is halo; or a pharmaceutically-acceptable salt thereof.

The phrase "further provided", as used in the above description, is intended to mean that the denoted proviso is not to be considered conjunctive with any of the other provisos.

Compounds of Formula I would be useful for the treatment of inflammation in a subject, and for treatment of other

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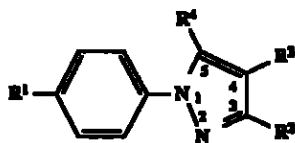
appropriate. The daily dose can be administered in one to four doses per day.

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, stonic 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 hydroxypropylmethyl 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 I



wherein R¹ is sulfamyl;

wherein R² is selected from hydrido, halo, haloalkyl, cyano, nitro, formyl, carboxyl, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, amido, alkoxy, amidoalkyl, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkyl-sulfamyl, N-arylsulfamyl, arylsulfonyl, N,N-dialkylsulfamyl, N-alkyl-N-arylsulfamyl and heterocyclic;

wherein R³ is selected from hydrido, alkyl, halo, haloalkyl, cyano, nitro, formyl, carboxyl, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, amido, alkoxy, amidoalkyl, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkyl-sulfamyl, N-arylsulfamyl, arylsulfonyl, dialkylsulfamyl, N-alkyl-N-arylsulfamyl, heterocyclic, heterocycloalkyl and aralkyl; and

wherein R⁴ is selected from aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R⁴ is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, amido, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, sulfamyl, N-alkyl-

sulfamyl, amino, N-alkylamino, N, N-dialkylamino, heterocyclic, nitro and acylamino;

provided R² and R³ are not identical radicals selected from hydrido, carboxyl and ethoxycarbonyl; further provided that R² is not carboxyl when R³ is hydrido and when R⁴ is phenyl; and further provided that R³ is not hydrido or alkyl when R² is haloalkyl;

or a pharmaceutically-acceptable salt thereof.

2. Compound of claim 1 wherein R¹ is sulfamyl; wherein R² is selected from hydrido, halo, haloalkyl, cyano, nitro, formyl, carboxyl, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, amido, alkoxy, amidoalkyl, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkylsulfamyl, N-arylsulfamyl, arylsulfonyl, N, N-dialkylsulfamyl, N-alkyl-N-arylsulfamyl and heterocyclic; wherein R³ is selected from alkyl, halo, haloalkyl, cyano, nitro, formyl, carboxyl, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, amido, alkoxy, amidoalkyl, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkylsulfamyl, N-arylsulfamyl, arylsulfonyl, N,N-dialkylsulfamyl, N-alkyl-N-arylsulfamyl, heterocyclic, heterocycloalkyl and aralkyl; and wherein R⁴ is selected from aryl, cycloalkyl, cycloalkenyl and heterocyclic; wherein R⁴ is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, amido, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, sulfamyl, N-alkylsulfamyl, amino, N-alkylamino, N, N-dialkylamino, heterocyclic, nitro and acylamino; or a pharmaceutically-acceptable salt thereof.

3. Compound of claim 2 wherein R² is hydrido or haloalkyl; wherein R³ is selected from alkyl, halo, carboxyalkyl, N-monoalkyl-N-hydroxyamido, N-monoalkyl-N-hydroxyamidoalkyl and N-monoalkylamido; and wherein R⁴ is aryl optionally substituted at a substitutable position with halo; or a pharmaceutically-acceptable salt thereof.

4. Compound of claim 3 wherein R² is selected from hydrido, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl; wherein R³ is selected from fluoro, chloro, bromo, methyl, ethyl, propyl, isopropyl, butyl, N-methylamido, N-ethylamido, N-isopropylamido, N-propylamido, N-butylamido, N-isobutylamido, N-terbutylamido, N-pentylamido, N-cyclohexylamido, N-cyclopentylamido, carboxypropyl, carboxymethyl, carboxyethyl, N-methyl-N-hydroxyamido, N-methyl-N-hydroxyamidomethyl, N-methyl-N-hydroxyamidoethyl and N-methyl-N-hydroxyamidopropyl; and wherein R⁴ is phenyl optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro and bromo; or a pharmaceutically-acceptable salt thereof.

5. Compound of claim 4 selected from compounds, and their pharmaceutically acceptable salts, of the group consisting of

- 4-[5-(4-bromophenyl)-3-(cyano)-1H-pyrazol-1-yl]benzenesulfonamide;
- 4-[5-(4-nitrophenyl)-3-(cyano)-1H-pyrazol-1-yl]benzenesulfonamide;
- 1-[4-(aminosulfonyl)phenyl]-5-(4-bromophenyl)-1H-pyrazole-3-carboxamide;

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: 1-16923

EDICTO No. 604

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió Resolución No. 34976 de 20-DIC-2006. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "DERIVADOS DE ETÉRES DE PIRAZOL COMO AGENTES ANTIINFLAMATORIOS ANALGESICOS".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Álvaro Correa Ordoñez, o a quien haga sus veces, en su calidad de apoderado de Pfizer Products Inc., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los 20 DIC. 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIME RUBIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:00 a.m. de hoy.

Secretaría General Ad-Hoc 10-ENE-2007
Secretaría General Ad-Hoc
EDICTO No. 604

Este edicto se desliza hoy 23-ENE-2007 a las 4:30 p.m.