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335

As 2352/P

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES

E S D

Ref Expediente No 00-058 781
Solicitud de Patente a nombre de
NOVARTIS AG

SUPERINDUSTRIA Y COMERCIO	
Radicacion	00058781 00083004 Folios 2
Fecha (AMB)	2003-03-12 17 03 51
Tramite	032 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia	2626 DIVISION DE NUEVAS CREACIONES

Yo, **JIMENA ESCOBAR URIBE**, identificada como aparece al pie de mi firma, domiciliada en Bogota, en la Carrera 11 A No 94-76 Of 305, obrando como apoderada de la sociedad **NOVARTIS AG**, domiciliada en Basilea, Suiza, solicitante de la patente de la referencia, pido a usted que se proceda a examinar si la invencion, cuya patente se tramita en el expediente de la referencia, es patentable

Adjunto al presente memorial el recibo No 03 - 888 de enero 7, 2003, por la suma de \$335 000 oo, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio

Señor Superintendente,


JIMENA ESCOBAR URIBE
C C 39 779 452 de usaquen
T P 68 228
Cod 5376
JEU/ra

2352



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Industria y Comercio

SUPERINTENDENCIA

NIT 80017.089-2

RECIBO OFICIAL DE CAJA 03 - 303
FECHA CIERRE DE 2003

SUPERINDUSTRIA Y COMERCIO		
Radicacion	00054781 00000004	Folios 2
Fecha (AMD)	2003 03-12 17 03 51	
Tramite	002 PATENTES D 1 REGISTRO/ 536 PETICION	
Dependencia	2820 DIVISION DE NUEVAS CREACIONES	

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº PAGO	FECHA PAGO	Vr PAGO
ESCEBAR JRIIBE ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	9022091	07/01/2003	6,426,000 00

***** CONCEPTO *****

CANT	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
50005-01-01	SOLICITUDES	8º EXAME, DE PATENTABILIDAD DE INVEN	335,000 00
		TOTAL	335,000 00

SOM TRESCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE

RECIBO DE CASH APLICADO AL EXPEDIENTE N.º

Carrera 13 No 27-00 Pisos 5 y 10
Conmutador 334 12 21
Fax 281 31 25
Santa Fe de Bogota DC Colombia

337-370

DIVISION DE NUEVAS CREACIONES

RADICACION EXPEDIENTE No **00 58781**

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION** FUE PUBLICADO

EN LA GACETA DE PROPIEDAD INDUSTRIAL No **525** DE FECHA **28 DE FEBRERO DE 2003**

EL TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL **29 DE MAYO DE 2003**

NOTA Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicacion en la gaceta de Propiedad Industrial debera solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono de acuerdo con lo establecido en el Articulo 44 de la Decision 486/2000

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS

SI _____ NO **X** _____

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES**

2020
Bogota, D C

Doctora
JIMENA ESCOBAR URIBE
(Apoderado)

ASUNTO	Radicacion	00058781	
	Tramite	002	
	Evento	001	
	Actuacion	430	8389
	Oficio		
	Folios	021	

Como resultado del examen de fondo realizado con fundamento en el articulo 45 de la Decision 486 de la Comision de la Comunidad Andina se le comunica

Documentos estudiados

Los textos estudiados fueron la descripcion (Folios 3 a 131) y las reivindicaciones 1 a 27 (Folios 132 a 162)

La presente solicitud reivindica prioridad británica N° GB9918684 3 de 09 de septiembre de 1999 y cumple con lo establecido en los articulos 9, 10 y 11 de la Decision 486 de la Comision de la Comunidad Andina

Objeto de invencion

La presente solicitud se titula Derivados de acido hidroxamico sustituidos por arilsulfonamido, compuestos y composiciones farmaceuticas que los contienen y procedimientos para su aplicacion y preparacion

El objeto de la presente solicitud se refiere a derivados de acido hidroxamico sustituidos por arilsulfonamido a procesos e intermediarios novedosos para su preparacion a composiciones farmaceuticas que comprenden estos derivados a composiciones farmaceuticas que comprenden inhibidores selectivos de MMP2, al uso de los derivados de acido hidroxamico como medicamentos a un metodo para el tratamiento de enfermedades dependientes de MMP, en particular MMP2, en particular enfermedades hiperproliferativas, o condiciones en mamiferos que respondan a la inhibicion de MMP, en particular MMP2, utilizando inhibidores selectivos de MMP2 en particular los derivados de acido hidroxamico de la formula I o a composiciones farmaceuticas que comprenden inhibidores selectivos de MMP2 en particular los derivados de acido hidroxamico de la formula I

Segun la descripcion los miembros de la familia enzimática de metaloproteinasas degradantes de matriz (MMP) tales como gelatinasa, estromelisin y colagenasa estan implicados en diferentes procesos biologicos, por ejemplo en la degradacion de la matriz del tejido (por ejemplo colapso de colageno) y en muchas condiciones patologicas que involucren tejido conectivo anormal y metabolismo de matriz de

membrana de basamento, tales como artritis (por ejemplo osteoartritis y artritis reumatoide) ulceración del tejido (por ejemplo ulceración cornea epidermica y gastrica) sanado anormal de heridas enfermedad periodontal enfermedad osea (por ejemplo enfermedad de Paget y osteoporosis) metastasis o invasion tumoral psoriasis, así como infección por VIH arteriosclerosis dilatación ventricular y restenosis en angioplastia

De acuerdo con la presente solicitud la selectividad es en general una característica conveniente de los compuestos farmacológicamente activos debido a que los efectos secundarios de los fármacos que comprendan compuestos selectivos son mas pequeños comparandose con los fármacos que comprendan compuestos menos selectivos Debido a que la familia de MMPs consiste en varias enzimas diferentes que están involucradas en diferentes procesos biológicos, es deseable tener inhibidores selectivos de MMPs singulares o subgrupos de la familia de enzimas MMP Los compuestos de la fórmula I y sus sales farmacéuticamente aceptables inhiben la metaloproteínasa degradante de matriz tal como gelatinasa estromelina y metaloelastasa de macrófagos, y las metaloproteinasas de matriz de tipo de membrana tales como MT1-MMP y MT2-MMP

Lo que se reivindica como novedoso es lo siguiente un derivado de ácido alfa-aminohidroxámico de la fórmula I (ver folio 132) y derivados de profármaco farmacéuticamente aceptables y sales farmacéuticamente aceptables del mismo

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/16 31/18

Claridad de la solicitud

El artículo 30 de la Decisión 486 de la Comisión de la Comunidad Andina establece que Las reivindicaciones definirán la materia que se desea proteger mediante la patente Deben ser claras y concisas y estar enteramente sustentadas por la descripción

Las reivindicaciones podrán ser independientes o dependientes Una reivindicación será independiente cuando defina la materia que se desea proteger sin referencia a otra reivindicación anterior Una reivindicación será dependiente cuando defina la materia que se desea proteger refiriéndose a una reivindicación anterior Una reivindicación que se refiera a dos o más reivindicaciones anteriores se considerará una reivindicación dependiente múltiple "

De acuerdo con lo anterior la reivindicación 1 (folios 132 y 133) y sus dependientes mencionan términos que conllevan a ambigüedad y subjetividad restandole claridad al objeto que se pretende proteger Por ejemplo "alquilo inferior" no se sabe cuantos carbonos tiene el alquilo y si es una cadena lineal o ramificada, "aminoalquilo inferior", "aciloxilo inferior" entre otros

Los significados para R son bastante amplios, es decir se refieren a grupos sencillos como alquilo C2-7 hasta grupos complejos como heterociclos sustituidos o no sustituidos que por lo demás no se dice que grupos son los sustituyentes de dichos anillos

Las reivindicaciones 24 a 27 (folios 161 y 162) que se refieren a un compuesto de fórmula II IV, V y VIII respectivamente, no son claras puesto que no se comprende si se trata de compuestos intermediarios ya que por ser reivindicaciones independientes no reflejan relación con las reivindicaciones anteriores

Excepciones de Patentabilidad

El artículo 20 de la Decisión 486 se establece No serán patentables a) las invenciones cuya explotación comercial en el territorio del País Miembro respectivo deba impedirse necesariamente para proteger el orden público o la moral. A estos efectos la explotación comercial de una invención no se considerará contraria al orden público o a la moral solo debido a la existencia de una disposición legal o administrativa que prohíba o que regule dicha explotación b) las invenciones cuya explotación comercial en el País Miembro respectivo deba impedirse necesariamente para proteger la salud o la vida de las personas o de los animales o para preservar los vegetales o el medio ambiente. A estos efectos la explotación comercial de una invención no se considerará contraria a la salud o la vida de las personas o de los animales o para la preservación de los vegetales o del medio ambiente solo por razón de existir una disposición legal o administrativa que prohíba o que regule dicha explotación c) las plantas los animales y los procedimientos esencialmente biológicos para la producción de plantas o animales que no sean procedimientos no biológicos o microbiológicos d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal así como los métodos de diagnóstico aplicados a los seres humanos o a animales

De acuerdo con lo anterior la(s) reivindicación(es) 15 a 17 (Folios 156 y 157), que se refiere(n) a un método para el tratamiento de condiciones o enfermedades asociadas con MMP2, no es (son) patentable(s)

Reivindicaciones de uso

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 procedimiento en todos los campos de la tecnología siempre que sean nuevas tengan nivel inventivo y sean susceptibles de aplicación industrial

De acuerdo con lo anterior, la(s) reivindicación(es) 20 a 22 (Folios 157 y 158) que se refiere(n) a el uso de un compuesto de la fórmula I de acuerdo con cualquiera de las reivindicaciones 1 a 12, no se encuentra(n) dentro del campo de la patentabilidad nombrado en el artículo 14

Determinación del estado de la técnica

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "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

Solo 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 este incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40"

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 09/08/1999 se buscaron documentos del estado de la técnica relacionados con fecha de publicación anterior a esta

Se hizo la búsqueda de documentos relevantes en el estado de la técnica, entendiendo como estado de la técnica la definición provista en el artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina y las excepciones fijadas en el artículo 17 de la misma

Se encontró como antecesoridades (documentos cuya fecha de publicación es anterior a la fecha de presentación de la primera solicitud de patente sobre la cual se reivindica prioridad o de la fecha de presentación de esta solicitud) que pueden

afectar la patentabilidad del objeto de la presente solicitud

Nº	Documento	Titulo	Fecha de Publicacion
1	US 5932695	Synthesis of hydroxamic acid dervatives	3 de agosto de 1999
2	WO 96/00214	Arylsulfonamido-substituted hydroxamic acids as matrix metalloproteinase inhibitors	4 de enero de 1996
3	WO 97/05865	C-proteinase inhibitors for the treatment of disorders related to the overproduction of collagen	20 de febrero de 1997
4	WO 99/06340	Acylic metalloprotease inhibitors	11 de febrero de 1999
5	EP 0915086	Phenylsulfonamide derivatives	12 de mayo de 1999
6	WO 99/07675	Aryloxyarylsulfonylamino hydroxamic acid derivatives	18 de febrero de 1999

Evaluacion de los requisitos de Patentabilidad

El Artículo 14 de la Decision 486 de la Comision de la Comunidad Andina el cual establece "Los Paises Miembros otorgaran Patentes para las invenciones sean de producto o de procedimiento en todos los campos de la tecnologia siempre que sean nuevas tengan nivel inventivo y sean susceptibles de aplicacion industrial

Se procedio a evaluar los requisitos de novedad, nivel inventivo y aplicacion industrial con el fin de establecer la patentabilidad de la invencion reivindicada en la solicitud en estudio

Evaluacion de Nivel Inventivo

El articulo 18 de la Decision 486 de la Comisión de la Comunidad Andina establece que "Se considerara que una invencion tiene nivel inventivo si para una persona del oficio normalmente versada en la materia tecnica correspondiente esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la tecnica"

El Nivel Inventivo se evaluo por comparacion entre lo solicitado y encontrado en el estado de la tecnica y que se relaciona con el objeto reivindicado y de acuerdo con la definicion de nivel inventivo del Artículo 18 de la Decision 486 de la Comision de la Comunidad Andina

La Solicitud de Patente Colombiana No 00058781 se refiere a

Un derivado de acido alfa-aminohidroxamico de la formula I (ver folio 132) y derivados de profarmaco farmaceuticamente aceptables y sales farmaceuticamente aceptables del mismo

Las anterioridades US 5932695 (folios 345 a 347), WO 96/00214 (folios 348 y 349), WO 97/05865 (folios 350 a 352), WO 99/06340 (folios 353 y 354), EP 0915086 (folios 355 a 357) y WO 99/07675 (folios 358 y 359) mencionan compuestos derivados de acido hidroxamico y que tienen actividad inhibitoria de metaloproteinasas que, por ende pueden emplearse en el tratamiento del cancer

El documento US 5932695 revela compuestos derivados de ácido hidroxámico muy semejantes a compuestos de la presente solicitud, y difieren estructuralmente de estos últimos en la presencia de un CH₂ entre el grupo SO₂ y anillo que se encuentran directamente unidos en la presente solicitud, además, dicho anillo no está sustituido, mientras que en la actual solicitud está sustituido por (OR)_n

El documento WO 96/00214 menciona compuestos derivados anilsulfonamido-hidroxámico cuya diferencia estructural con respecto a los compuestos de la presente solicitud está en la sustitución del anillo unido a SO₂

El documento WO 97/05865 menciona compuestos derivados de ácido hidroxámico que presentan una estructura química muy semejante a la de los compuestos de la actual solicitud. Las diferencias fundamentales están en que tienen un grupo hidroxámico adicional y el anillo unido a SO₂ no está sustituido. Las sustituciones del nitrógeno central de la presente solicitud están contempladas dentro de esta anterioridad.

En el documento WO 99/06340 se contempla la posibilidad de sustitución del anillo unido a SO₂, al igual que en el documento EP 0915086, y en el documento WO 99/07675 se especifica dicha sustitución, que corresponde a una de las opciones reveladas en la actual solicitud de patente.

Juntando la información encontrada en el estado de la técnica, una persona medianamente versada en la materia resolvería fácilmente el problema técnico planteado por la presente solicitud. Además, se aprecia que no hay un salto importante en la tecnología conocida en este tema de los derivados de ácido hidroxámico que tienen actividad contra el cáncer, inhibiendo metaloproteinasas de matriz.

La respuesta al problema técnico que se pretendía resolver resulta obvia partiendo de las anterioridades citadas.

Como se observa, el objeto de esta solicitud podría resultar obvio para una persona del oficio normalmente versada en la materia y derivarse de manera evidente del estado de la técnica.

Evaluación de la Aplicación Industrial

El artículo 19 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Se considerará que una invención es susceptible de aplicación industrial cuando su objeto pueda ser producido o utilizado en cualquier tipo de industria, entendiéndose por industria la referida a cualquier actividad productiva, incluidos los servicios".

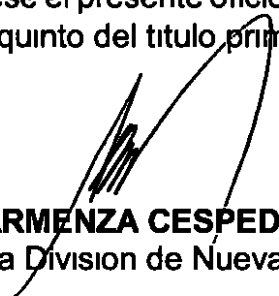
El objeto de la presente solicitud cumple con el requisito de Aplicación Industrial.

En conclusión, los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	US 5932695	1 a 14, 18, 19, 23 a 27	Nivel Inventivo
2	WO 96/00214	1 a 14, 18, 19, 23 a 27	Nivel Inventivo
3	WO 97/05865	1 a 14, 18, 19, 23 a 27	Nivel Inventivo
4	WO 99/06340	1 a 14, 18, 19, 23 a 27	Nivel Inventivo
5	EP 0915086	1 a 14, 18, 19, 23 a 27	Nivel Inventivo
6	WO 99/07675	1 a 14, 18, 19, 23 a 27	Nivel Inventivo

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


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 15 SET 2005

CONCEPTO TECNICO N° 1401	EXAMINADOR TECNICO Código N° 202005	EXAMINADOR JURIDICO Codigo N°
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345
344



US005932695A

United States Patent [19]
Floyd et al

[11] **Patent Number** **5,932,695**
[45] **Date of Patent** ***Aug 3, 1999**

[54] **SYNTHESIS OF HYDROXAMIC ACID DERIVATIVES**

4,868,248 9/1989 Sparapany 525/380

[75] **Inventors** **Christopher David Floyd**
Christopher Norman Lewis both of
Oxford United Kingdom

FOREIGN PATENT DOCUMENTS

0216499 4/1987 European Pat Off
0514648 11/1992 Europe in Pat Off
0561722 9/1993 European Pat Off

[73] **Assignee** **British Biotech Pharmaceuticals Ltd**
Oxford United Kingdom

OTHER PUBLICATIONS

[*] **Notice** This patent issued on a continued prosecution application filed under 37 C.F.R. 1.53(d) and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2)

International Search Report for PCT/GB96/00428
PCT Written Opinion for PCT/GB96/00428
Letter by Applicant in reply to PCT written opinion for PCT/GB96/00428
PCT International Preliminary Examination Report for PCT/GB96/00428
(1) Chemical Abstracts vol 77 No 24 Dec 11 1972 Abstract No 153114c Chernyshev VP Maleic Anhydride Copolymer p 39 col 2 & SU A 342 865 (Institute of Fine Chemical Technology Moscow) Jun 22 1972
(2) Polymer Bulletin vol 32 No 3 1994 pp 273-279 XP002003868 Jack Seung Lee Synthesis of Porous Poly (Hydroxamic Acid) from Poly(Ethyl Acrylate-Co-Divinyl benzene)

[21] **Appl No** **08/809,499**

[22] **PCT Filed** **Feb 26, 1996**

[56] **PCT No** **PCT/GB96/00428**

§ 371 Date **Mar 24, 1997**

§ 102(c) Date **Mar 24, 1997**

[87] **PCT Pub No** **WO96/26223**

PCT Pub Date Aug 29, 1996

[30] **Foreign Application Priority Data**

Feb 24 1995 [GB] United Kingdom 9503749

[51] **Int Cl⁶** **C07K 1/04 C08G 63/48**

[52] **U.S. Cl.** **530/333 530/331 530/334**
525/5411 525/374 525/377

[58] **Field of Search** **530/331 333**
530/334 525/5411 374 377

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,461,876 7/1984 Ticherman 525/374

Primary Examiner—Bennett Celsa
Attorney Agent or Firm—Hale and Dorr LLP

[57] **ABSTRACT**

This invention is directed to a solid phase reaction product of a solid substrate carrying a plurality of covalently bound hydroxylamine or protected hydroxylamine groups. The solid solid phase reaction product may be used for the synthesis of hydroxamic acid derivatives or a combinatorial library of such compounds.

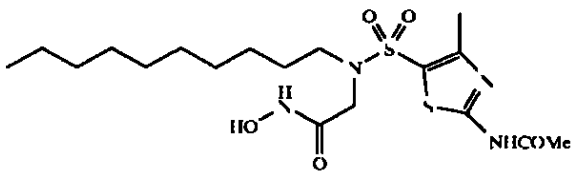
12 Claims, No Drawings

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enzymes. Those pools showing the greatest inhibitory activity were then subjected to an iterative deconvolution procedure to identify individual active inhibitors.

Example C

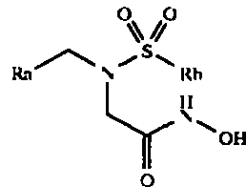
Use of the resin from Example 1 in the preparation of a sulfonamide hydroxamate derivative 2 (N-Decyl 2-acetamido-4-methylthiazol-5-ylsulfonamido) aceto hydroxamic acid.



Bromoacetic acid (167 mg, 1.2 mmol) and diisopropyl carbodiimide (94 mm³, 0.6 mmol) were added to a suspension of the resin (4 (O-methylhydroxylamine) phenoxy methyl copoly(styrene 1% divinylbenzene) resin (100–200 mesh)) prepared according to Example 1 (250 mg, 0.1 mmol) in DMI (6 cm³). The mixture was agitated for 90 minutes and then the solution was drained from the resin which was washed and dried as described above in Example 1. The resin was soaked in DMSO (2 cm³) and a solution of n-decylamine in DMSO (5 cm³ of a 2M solution, 10 mmol) was added and the mixture shaken for 4 h before the resin was drained and washed thoroughly as before. The resin was then suspended in DMI and 2-acetamido-4-methyl-5-thiazol-sulfonyl chloride (102 mg, 0.4 mmol) was added. The mixture was heated at 60° for 8 h and then the resin was drained, washed and dried as described previously. Cleavage from the resin as in Example A gave a white solid which was purified by column chromatography (10% methanol dichloromethane/silica) to give the desired 2 (N-decyl 2-acetamido-4-methylthiazol-5-ylsulfonamido) aceto hydroxamic acid (23 mg, 51%) as a white solid. ¹H NMR (CDCl₃) δ 3.83 (2H, m), 3.05 (2H, m), 2.72 (3H, s, Me), 2.35 (3H, s, NHCOMe), 1.69 (2H, m), 1.15–1.25 (14H, m, alkyl), 0.87 (3H, t, 1=7.2 Hz, CH₃ alkyl).

Example D

Use of the resin from Example 1 in the preparation of an array of sulfonamide hydroxamate inhibitors of matrix metalloproteinases.



Sulfonamide hydroxamic acid derivatives were prepared as a combinatorial array of individual compounds in purity sufficient for first throughput assays. The resin (4 (O-methylhydroxylamine) phenoxy methyl copoly(styrene 1% divinylbenzene) resin (100–200 mesh)) was loaded with bromoacetic acid as described in Example C. Elemental analysis of this different batch of resin confirmed that coupling had taken place. C 83.34, H 7.04, N 0.96, Br > 40% and suggested a loading of 0.65 mmol/g of this resin was

22

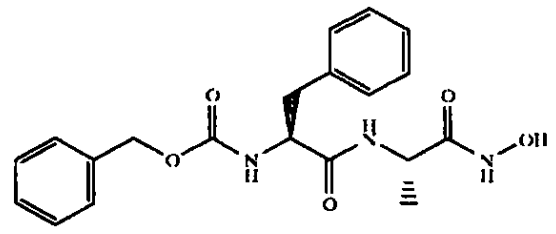
placed in each of 36 plastic Econopac tubes (BioRad) and swelled in DMI (5 cm³). The excess DMI was drained off and the tubes grouped into nine groups of four tubes. A solution (5 cm³ of a 2M solution in either DMI or DMSO) of one of the amines benzylamine, 4-methylbenzylamine, 4-methoxybenzylamine, 4-fluorobenzylamine, 4-chlorobenzylamine, pyridin-3-ylmethylamine, thien-2-ylmethylamine, furan-2-ylmethylamine and 3,4-dioxymethylbenzylamine was each added to each of four tubes (within one of the nine groups) which were then sealed and mixed thoroughly for 2 h. The solvent was removed, the resin washed as in Example C and reswelled in DMI. The tubes were regrouped into four groups each of nine tubes. Following a protocol analogous to that used in Example C, a DMI solution of 10 equivalents of one of the sulfonamide chlorides 3-chloropropylsulfonyl chloride, hexylsulfonyl chloride, octylsulfonyl chloride and decylsulfonyl chloride was added to each of the nine tubes (within one of the four groups) so that all 36 combinations of sulfonamides were prepared. After removal of the solvent by filtration, thorough washing with DMI, methanol and dichloromethane as above and drying under vacuum for several hours, the products were cleaved from the resin as in Example C directly into plastic centrifuge tubes. The H₂O was removed by centrifugal evaporation and the resulting hydroxamic acids lyophilized from aqueous acetonitrile. All samples gave positive ferric chloride spots on TLC analysis {10% methanol in DCM/silica} (Table). All 36 samples were submitted for assay as inhibitors of metalloproteinases from which active compounds were identified.

TABLE

TLC {10% methanol in DCM/silica} R _f values for the compounds of Example D				
Ra	Rb			
	—(CH ₂) ₃ Cl	—C ₆ H ₅	—C ₆ H ₁₇	—C ₁₀ H ₂₁
C ₆ H ₅ —	0.25	0.2	0.45	0.45
4-MeC ₆ H ₄ —	0.35	0.4	0.4	0.4
4-MeOC ₆ H ₄ —	0.5	0.35	0.5	0.4
4-FC ₆ H ₄ —	0.3	0.3	0.5	0.5
4-ClC ₆ H ₄ —	0.15	0.2	0.4	0.4
pyridin-3-yl	0.0	0.05	0.0	0.05
thien-2-yl	0.1	0.3	0.1	0.6
furan-2-yl	0.1	0.3	0.1	0.4
3,4-(CH ₂) ₂ O C ₆ H ₄ —	0.3	0.4	0.5	0.45

Example E

Use of the resin from Example 2 in the preparation of a peptide hydroxamate derivative. Benzylloxycarbonyl-L-phenylalanyl-L-alanylhydroxamic acid.



Fmoc-Alanine (187 mg, 0.6 mmol), HOBT (92 mg, 0.6 mmol) and IBTU (194 mg, 0.6 mmol) were dissolved together in DMI (5 cm³). Diisopropylethylamine (0.183

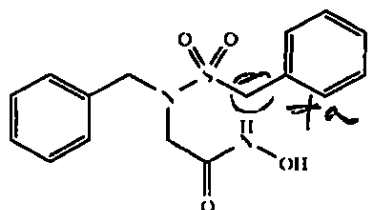
23

cm³ 1.05 mmol) was added and the resulting solution added to pre swelled (in DMI) modified resin from Example 2 (O hydroxylamine 2 chlorotriethyl copoly (styrene 1% divinylbenzene) resin (200-400 mesh)) (100 mg 0.15 mmol) and the mixture was then shaken gently together for 12 h. The resulting resin was then filtered washed thoroughly with DMF and treated with 20% piperidine in DMF (7 cm³) for 30 minutes. After removal of the solvent and thorough washing as described in Example 1 the resin was resuspended in DMI (1 cm³). A solution of Z phenylalanyl 1-alanylhydroxamic acid (180 mg 0.6 mmol) HOBT (92 mg, 0.6 mmol) and diisopropylcarbodiimide (94 mm³ 0.6 mmol) in DMI (5 cm³) was added and the resin suspension was gently agitated overnight by which time the initially blue staining of BPIB had been discharged. The resin was then drained and washed as described in Example 1 and dried in vacuo. It had a (KBr) 1668 (s) cm⁻¹.

The resin from above was suspended in a 20% solution of HIA in dichloromethane containing 1% (v/v) of triethylsilane under argon (5 cm³) for 45 minutes. The solution was removed from the resin by filtration the resin washed with a further portion (1 cm³) of the cleavage mixture the filtrate and washings combined and evaporated to leave benzyloxycarbonyl L phenylalanyl 1-alanylhydroxamic acid as a white solid. N C analysis indicated a single compound R_f 0.45 (10% methanol in dichloromethane) which gave a positive ferric chloride test. ¹H NMR (CDCl₃) δ 1.36 (3H d J=9 Hz Me alanine) 3.12 (2H m CH₂Ph) 4.14 (1H m CH) 4.4 (1H m CH) 5.13 (2H brs OCH₂Ph) 7.71-7.33 (~1 OH m aromatic) 7.8 (1H d NH).

Example 1

Use of the resin from Example 3 in the preparation of a sulfonamide hydroxamate derivative 2 (N Benzyl benzylsulfonamido) aceto hydroxamic acid



The resin of Example 3 (4 [4 (O methylhydroxylamine) 3 methoxyphenoxy] (N 4 methylbenzylhydrazyl)butyramide copoly(styrene 1% divinylbenzene) resin (100-200 mesh)) (0.5 g) was suspended in DMI (3 cm³). Diisopropylcarbodiimide (0.3 cm³) was added to a solution of bromoacetic acid (670 mg) in DMI (3 cm³) and after 3 minutes the resulting solution was added to the resin suspension and gently mixed together for 2 h. The resin was collected by filtration and washed thoroughly with DMF methanol methanol dichloromethane dichloromethane and ether. It was then dried in vacuo at 45° C for 18 h. Elemental analysis of the resin suggested a loading of 0.66 mmol/g. C 79.11 H 6.78 N 2.08 Br 5.25%.

The resin from above swelled in DMF (3 ml) was treated with (0.33 cm³ 3 mmol) benzylamine and gently agitated at room temperature overnight. The solvent was removed by filtration and the resin washed as described above in Example 1 and dried. The resin was swelled in DMF (3 ml) and phenylmethylsulfonyl chloride (0.8 g 4 mmol) was added and the mixture was gently agitated for 2 h at room

24

temperature. The resin was filtered and washed as described above in Example 1 and dried. A solution of 1% HIA in DCM (3 ml) was added to the resin at room temperature and the mixture gently agitated for 1 h. The resin was filtered and washed with DCM methanol and DCM the filtrates combined and evaporated under reduced pressure to give crude 2 (N benzyl benzylsulfonamido) aceto hydroxamic acid (0.39 g). TLC ferric chloride positive spot R_f 0.15 (10% methanol in DCM/silica).

Example 6

Use of the resin from Example 4 in the preparation of a sulfonamide hydroxamate derivative 2 (N Benzyl benzylsulfonamido) aceto hydroxamic acid

This resin of Example 4 (4 (2,4-dimethoxyphenyl O methylhydroxylamine) phenoxy methyl copoly (styrene 1% divinylbenzene) resin (100-200 mesh)) (0.25 g) was suspended in DMF (3 cm³). Diisopropylcarbodiimide (0.24 cm³) was added to a solution of bromoacetic acid (420 mg) in DMI (3 cm³) and after 3 minutes the resulting solution was added to the resin suspension and gently mixed together for 2 h. The resin was collected by filtration and washed thoroughly with DMF methanol methanol dichloromethane dichloromethane and ether. It was then dried in vacuo at 45° C for 18 h. Elemental analysis of the resin suggested a loading of 0.58 mmol/g. C 84.31 H 7.28 N 0.82 Br 4.65%.

Following the procedure of Example 6 the above resin was treated in turn with benzylamine and phenylmethylsulfonyl chloride. A solution of 10% acetic acid in DCM (3 ml) was added to the resin at room temperature and the mixture gently agitated for 2 h. The resin was filtered and washed with DCM methanol and DCM the filtrates combined and evaporated under reduced pressure to give crude 2-(N benzyl benzylsulfonamido) aceto hydroxamic acid (0.22 g).

Example 11

Use of the resin from Example 5 in the preparation of a peptide hydroxamate derivative Benzoyloxycarbonyl L prolyl L leucyl L alanylhydroxamic acid

Using procedures analogous to those described in Example A, the tripeptide Z-L prolyl L leucyl L alanyl was synthesised attached to the resin of Example 5 (4 [4 (1 aminoxyethyl) 2 methoxy 5 nitrophenoxy] (N4 methylbenzylhydrazyl) butyramide copoly (styrene 1% divinylbenzene) resin (100-200 mesh)). Following drying the elaborated resin (50 mg) in acetonitrile (1.5 cm³) was blanketed with argon in a stoppered reaction vial. The vial was placed 5 cm away from a 365 nm light source and irradiated for 15 h. TLC of the resulting solution indicated a ferric chloride positive component with R_f equivalent to that of the tripeptide hydroxamic acid of Example A. HPLC of the solution identified the desired tripeptide as the major product of the reaction along with an unidentified non hydroxamic acid component.

We claim

1. A solid phase reaction product comprising a solid substrate that is substantially insoluble in aqueous or organic reaction media wherein the solid substrate comprises a base substrate carrying a plurality of covalently bound hydroxylamine or protected hydroxylamine groups of formula (A)

348
347

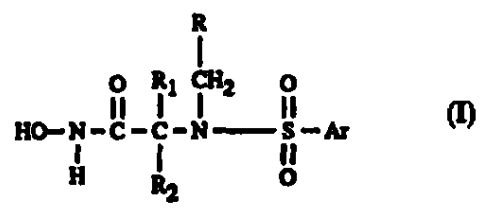


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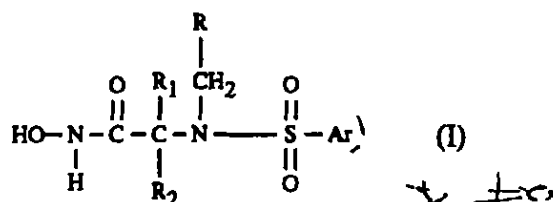
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ C07D 213/42, 223/10, 211/34, A61K 31/44, 31/18, C07D 405/12, 401/12, C07C 311/29, C07D 307/16, 313/18		A1	(11) International Publication Number WO 96/00214 (43) International Publication Date 4 January 1996 (04 01 96)
(21) International Application Number PCT/IB95/00464 (22) International Filing Date 12 June 1995 (12 06 95) (30) Priority Data 08/265 296 24 June 1994 (24.06 94) US (60) Parent Application or Grant (63) Related by Continuation US 08/265 296 (CIP) Filed on 24 June 1994 (24 06 94)		(74) Common Representative CIBA-GEIGY AG Patentabteilung Klybeckstrasse 141 CH-4002 Basle (CH) (81) Designated States AM AU BB BG BR, BY CA, CN CZ EE, FI GE, HU IS JP KG KP KR KZ LK LR, LT LV MD MG MN MX NO NZ, PL RO RU, SG SI SK, TJ TM TT UA US UZ VN European patent (AT BE, CH, DE, DK ES 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) ARIPO patent (KE, MW, SD SZ, UG) Published <i>With international search report</i>	
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(54) Title ARYLSULFONAMIDO SUBSTITUTED HYDROXAMIC ACIDS AS MATRIX METALLOPROTEINASE INHIBITORS			
(57) Abstract Compounds of formula (I) wherein R R ₁ R ₂ and Ar are as defined in the specification have valuable pharmaceutical properties and are effective especially as matrix metalloproteinase inhibitors for example for the treatment of arthritis They are prepared in a manner known per se.			



Claims

1 A compound of formula I



wherein

Ar is carbocyclic or heterocyclic aryl,

R is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C₃-C₇-cycloalkyl C₃-C₇-cycloalkyl-lower alkyl, (oxa or thia)-C₃-C₆-cycloalkyl, [(oxa or thia)-C₃-C₆-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl,

R₁ is C₈-C₁₀-cycloalkyl, (N-acyl-piperidyl)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, N-acyl or N-lower alkylpiperidyl)-(hydroxy or lower alkoxy)-lower alkyl, pyrrolidinyl, hexahydroazepinyl, N-lower alkyl-(hexahydroazepinyl or pyrrolidinyl), N-acyl-(hexahydroazepinyl, piperidyl or pyrrolidinyl) C₅-C₁₀-oxacycloalkyl, C₅-C₁₀-thiacycloalkyl, (hydroxy or oxo)-C₅-C₁₀-cycloalkyl, (hydroxy or oxo)-C₅-C₁₀-thiacycloalkyl, (hydroxy or oxo)-C₅-C₁₀-oxacycloalkyl, (amino, mono- or di-lower alkylamino or acylamino)-C₅-C₁₀-cycloalkyl, 2-oxo-(pyrrolidinyl, piperidyl or hexahydroazepinyl),

R₂ is hydrogen or lower alkyl,

a pharmaceutically acceptable prodrug derivative thereof, or a pharmaceutically



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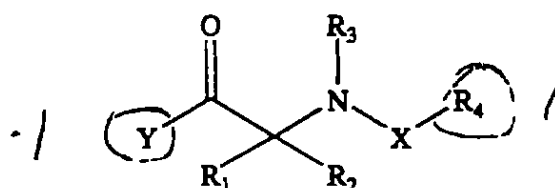
(51) International Patent Classification ⁶ A61K 31/215, 31/38, 31/40, 31/66, 31/165, 31/70, 31/34		A1	(11) International Publication Number WO 97/05865
			(43) International Publication Date 20 February 1997 (20 02 97)
(21) International Application Number PCT/US96/12876		(74) Agents HALLUIN Albert P et al Pennie & Edmonds 1155 Avenue of the Americas New York NY 10036 (US)	
(22) International Filing Date 8 August 1996 (08 08 96)			
(30) Priority Data 60/002 038 8 August 1995 (08 08 95) US 601 203 14 February 1996 (14 02 96) US 609 187 1 March 1996 (01 03 96) US		(81) Designated States AL AM AU AZ BB BG BR BY CA CN CU CZ, EE FI GE HU IL IS JP KG KP KR KZ LK LR LS LT LV MD MG MK MN MX NO NZ PL, RO RU SG SI SK TJ TM TR TT UA US 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 BJ CF CG CI CM GA GN ML MR NE SN TD TG)	
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(54) Title C PROTEINASE INHIBITORS FOR THE TREATMENT OF DISORDERS RELATED TO THE OVERPRODUCTION OF COLLAGEN			
(57) Abstract The present invention relates to the novel use of organic molecules capable of inhibiting C proteinase activity in order to regulate modulate and/or inhibit abnormal collagen formation			

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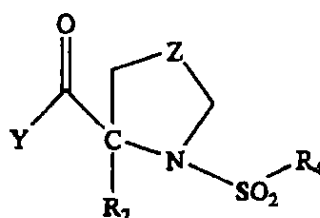
CLAIMS

What Is Claimed

1 A compound having an inhibitory effect on C-proteinase, said compound having a formula selected from the group consisting of



or



and pharmaceutically acceptable salts thereof,

wherein

R₁ is selected from the group consisting of H, lower alkyl, mono- or poly-haloalkyl, carboxyalkyl, aryl, heteroaryl, aralkyl, halo substituted aralkyl, heteroaralkyl, biaryl, biarylalkyl, hydroxyalkyl, alkoxyalkyl, acyloxyalkyl, mercaptoalkyl, (amino, mono- or dialkylamino)alkyl, acylaminoalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, alkyl-(thio, sulfinyl or sulfonyl)-alkyl,

R₂ is selected from the group consisting of H, lower alkyl,

R₃ is selected from the group consisting of H, lower alkyl, mono- or poly-haloalkyl, carboxyalkyl, aryl, heteroaryl, aralkyl, halo substituted aralkyl, heteroaralkyl, biaryl, biarylalkyl, hydroxyalkyl, alkoxyalkyl, acyloxyalkyl, mercaptoalkyl, (amino, mono- or dialkylamino)alkyl, acylaminoalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, alkyl-(thio, sulfinyl or sulfonyl)-alkyl

R_1 is selected from the group consisting of aryl, heteroaryl, alkyl
aralkyl, heteroaralkyl alkylamino, arylalkylamino

X is selected from the group consisting of SO_2 , $C=O$,

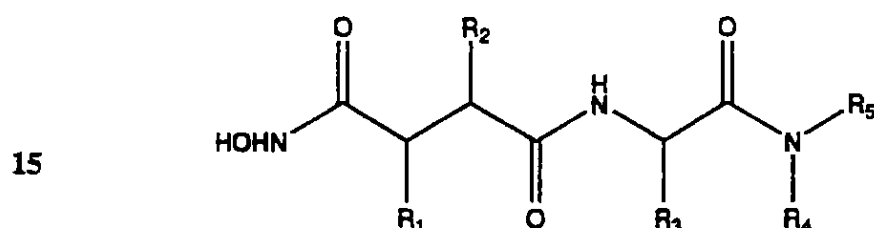
Y is selected from the group consisting of OH , $HOHN$ (hydroxylamine)

5 H_2N alkylamino,

Z is a direct bond, methylene, oxygen sulfur, amino, and

n is 0 or 1

2 A compound having an inhibitory effect on C-proteinase said
10 compound having a formula selected from the group consisting of



and pharmaceutically acceptable salts thereof,

wherein

20 R_1 is selected from the group consisting of H, lower alkyl, mono- or
poly-haloalkyl, carboxyalkyl, aryl heteroaryl aralkyl, heteroaralkyl, biaryl,
biarylalkyl, hydroxyl, hydroxyalkyl, alkoxyalkyl, acyloxyalkyl, mercaptoalkyl
(amino, mono- or dialkylamino)alkyl, acylaminoalkyl, cycloalkyl,
heterocycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl alkyl-(thio, sulfinyl or
sulfonyl)-alkyl,

25 R_2 is selected from the group consisting of H, lower alkyl mono- or
poly-haloalkyl carboxyalkyl aryl heteroaryl aralkyl, heteroaralkyl, biaryl,
biarylalkyl, hydroxyl hydroxyalkyl, alkoxyalkyl, acyloxyalkyl, mercaptoalkyl
(amino, mono or dialkylamino)alkyl, acylaminoalkyl, cycloalkyl,
heterocycloalkyl, cycloalkylalkyl heterocycloalkylalkyl, alkyl-(thio, sulfinyl or
30 sulfonyl)-alkyl,

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number PCT/IB98/01139		(74) Agents REED T David et al The Procter & Gamble Company 5299 Spring Grove Avenue Cincinnati OH 45217 (US)
(22) International Filing Date 27 July 1998 (27 07 98)		
(30) Priority Data 60/054 348 31 July 1997 (31 07 97) 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 GE GH GM HU ID 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 SL, TJ TM TR TT UA UG UZ VN YU ZW ARIPO patent (GH GM KE LS MW SD SZ UG ZW) Eurasian patent (AM AZ BY KG KZ MD RU TJ TM) European patent (AT BE, CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE) OAPI patent (BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG)
(71) Applicant THE PROCTER & GAMBLE COMPANY [US/US] One Procter & Gamble Plaza Cincinnati OH 45202 (US)		
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(54) Title ACYCLIC METALLOPROTEASE INHIBITORS		
(57) Abstract The invention provides compounds of formula (I) as described in the claims or an optical isomer diastereomer or enantiomer thereof or a pharmaceutically-acceptable salt or biohydrolyzable amide ester or imide thereof are useful as inhibitors of metalloproteases. Also disclosed are pharmaceutical compositions and methods of treating diseases disorders and conditions characterized by metalloprotease activity using these compounds or the pharmaceutical compositions containing them		
(I)		
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SUPERINTENDENCIA

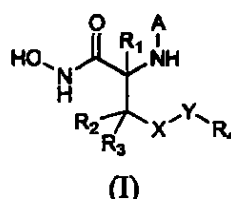
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60

WHAT IS CLAIMED IS

- 1 A compound having a structure according to Formula (I)



wherein

A is SO_2Ar , COAr , CONHAr , PORAr , where Ar is monocyclic or bicyclic aromatic or a monocyclic or bicyclic heteroaromatic, substituted or unsubstituted,

R_1 is alkyl or hydrogen,

R_2 , R_3 , and R_4 are each independently chosen from hydrogen, alkyl, aryl, heteroaryl, aryl-alkyl, alkoxy-alkyl, heterocycle, heterocycle alkyl, and these substituents may be substituted or unsubstituted, rings can be formed by R_2 and R_3 , R_1 and R_2 or R_3 and R_4 .

X is a bond, a $(\text{C}_1\text{-C}_6)$ alkyl, CO, or a heteroatom chosen from O, N, NZ, S, SO, or SO_2 ,

Y is a bond, a $(\text{C}_1\text{-C}_6)$ alkyl, CO, CO_2 , CONH, or a heteroatom chosen from O, N, NZ, S, SO, or SO_2 , and

Z is hydrogen, COR_4 , COOR_4 , CONHR_4 , R_4CSR_4 , CSNHR_4 , and SO_2R_4

This structure also includes an optical isomer, diastereomer or enantiomer for Formula (I), or a pharmaceutically-acceptable salt, or biohydrolyzable amide, ester, or imide thereof, an optical isomer, diastereomer or enantiomer for Formula (I), or a pharmaceutically-acceptable salt or biohydrolyzable amide, ester, or imide thereof

- 2 The compound of Claim 1, wherein A is SO_2Ar , and Ar is phenyl, substituted phenyl or substituted biphenyl and the substitution is with hydroxy, alkoxy, phenoxy, nitro, halo or phenyl

- 3 The compound of Claim 4, wherein Ar is substituted at the ortho or para position relative to the attachment of Ar to the molecule

- 4 The compound of Claim 1, wherein R_1 is H, and R_2 and R_3 can form a 3-9 substituted or unsubstituted membered ring containing from 0 to 4 heteroatoms, chosen from O, N, NZ, S, SO, or SO_2

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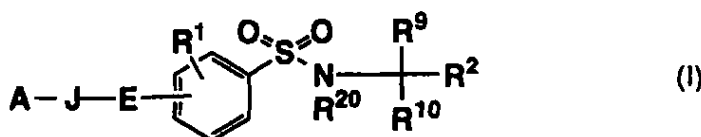
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(54) **PHENYLSULFONAMIDE DERIVATIVES**

(57) A phenylsulfonamide derivative of formula (I)



(wherein R¹ is H alkyl R² is COOR³ CONHOR⁴ E is vinylene ethynylene A is H alkyl a carbocyclic ring a heterocyclic ring J is a single bond alkylene R⁹ R¹⁰ is H (substituted) alkyl COR¹¹ a carbocyclic ring a heterocyclic ring etc R²⁰ is H (substituted) alkyl etc) and a non toxic salt thereof and a process for the preparation thereof a matrix metalloproteinase inhibitor containing a compound above and an agent for prevention and/or treatment of rheumatoid diseases arthrositis unusual bone resorption osteoporosis periodontitis, interstitial nephritis arteriosclerosis pulmonary emphysema cirrhosis cornea injury metastasis or invasion of tumor cells a disease induced by proliferation of tumor cells an autoimmune disease (Crohn's disease or Sjogren's syndrome) diseases caused by vascular emigration and infiltration of leukocytes or arterIALIZATION

EP 0 915 086 A1

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EP 0 915 086 A1

(continued)

Magnesium stearate (lubricating agent)	0.1 g
Micro crystalline cellulose	4.7 g

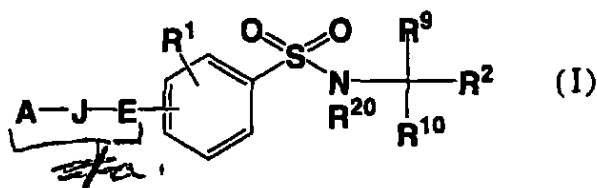
Formulation Example 2

[0264] The following components were admixed in conventional method. The solution was sterilized in conventional manner, placed in 5 ml portions into ampoules and freeze-dried in conventional method to obtain 100 ampoules each containing 20 mg of active ingredient.

N [4 [2 (4 Methylphenyl)ethynyl]phenylsulfonyl] D phenylalanine	2.0 g
Mannitol	20 g
Distilled water	500 ml

Claims

1. A phenylsulfonamide derivative of formula (I)



(wherein R¹ is hydrogen or C₁₋₄ alkyl
R² is COOR³ or CONHOR⁴
R³ is

- 1) hydrogen
- 2) C₁₋₈ alkyl
- 3) phenyl or
- 4) C₁₋₄ alkyl substituted by a group selected from phenyl -OCOR¹⁵ (wherein R¹⁵ is C₁₋₄ alkyl) and CONR¹⁶R¹⁷ (wherein R¹⁶ and R¹⁷ are each independently hydrogen or C₁₋₄ alkyl)

R⁴ is hydrogen, C₁₋₈ alkyl, phenyl or C₁₋₄ alkyl substituted by phenyl
E is



A is hydrogen, C₁₋₈ alkyl, a carbocyclic ring or a heterocyclic ring in which the said rings may be substituted by 1-3 groups selected from

C₁₋₁₅ alkyl, C₁₋₁₅ alkoxy, halogen, nitro, cyano, guanidino, amidino, hydroxy, benzyloxy, trifluoromethyl, NR⁵R⁶ (wherein R⁵ and R⁶ are each independently hydrogen, C₁₋₄ alkyl or COOR⁷ (wherein R⁷ is C₁₋₄ alkyl or benzyl)), -COOR⁸ (wherein R⁸ is hydrogen, C₁₋₄ alkyl, phenyl or C₁₋₄ alkyl substituted by phenyl), a carbocyclic ring and a heterocyclic ring or C₁₋₄ alkyl substituted by hydroxy, C₁₋₄ alkoxy, NR⁵R⁶, a carbocyclic ring or a heterocyclic ring.

J is a single bond or C₁₋₈ alkylene
R⁹ and R¹⁰ are each independently

- (1) hydrogen

357
356

EP 0 915 086 A1

- (2) C₁₋₈alkyl (wherein one carbon atom may be replaced by a sulfur atom)
(3) COR¹¹ (wherein R¹¹ is hydroxy C₁₋₈alkyl C₁₋₈alkoxy phenoxy C₁₋₄alkoxy substituted by phenyl or NR¹⁸R¹⁹ (wherein R¹⁸ and R¹⁹ are each independently hydrogen C₁₋₄alkyl phenyl or C₁₋₄alkyl substituted by 1-2 phenyl in which the said phenyl may be substituted by 1-3 groups selected from C₁₋₄alkyl C₁₋₄alkoxy halogen hydroxy and trifluoromethyl))
(4) a carbocyclic ring
(5) a heterocyclic ring or
(6) C₁₋₈alkyl substituted by a group selected from (i) (viii) below

- (i) COR¹¹ wherein R¹¹ is as defined above
(ii) C₁₋₄alkoxy
(iii) hydroxy
(iv) benzyloxy
(v) guanidino
(vi) NR¹²R¹³ (wherein R¹² and R¹³ are each independently hydrogen C₁₋₄alkyl or COOR¹⁴ (wherein R¹⁴ is C₁₋₄alkyl or benzyl))
(vii) a carbocyclic ring
(viii) a heterocyclic ring
(in which the carbocyclic ring or the heterocyclic ring defined above may be substituted by 1-3 groups selected from C₁₋₄alkyl C₁₋₄alkoxy halogen hydroxy and trifluoromethyl)

R²⁰ is hydrogen C₁₋₄alkyl C₁₋₈alkoxycarbonyl C₁₋₄alkoxycarbonyl substituted by phenyl or C₁₋₈alkyl substituted by a group selected from hydroxy C₁₋₄alkoxy benzyloxy COOR²¹ (wherein R²¹ is hydrogen C₁₋₈alkyl or benzyl) NR²²R²³ (wherein R²² and R²³ are each independently hydrogen or C₁₋₄alkyl) a carbocyclic ring and a heterocyclic ring or R⁹ and R²⁰ together with the carbon atom and nitrogen atom to which they are attached represent a 5-7 membered heterocyclic ring containing one nitrogen) or a non toxic salt thereof

- 2 A compound according to claim 1 wherein R² is COOR³ (wherein R³ is as defined in claim 1)
3 A compound according to claim 1 wherein R² is CONHOR⁴ (wherein R⁴ is as defined in claim 1)
4 A compound according to claim 1 wherein A is hydrogen or C₁₋₈alkyl
5 A compound according to claim 1 wherein A is a carbocyclic ring or a heterocyclic ring
6 A compound according to claim 1 which is

- (1) N [4 (1-pentynyl)phenylsulfonyl] D-alanine
(2) N [4 (1-heptynyl)phenylsulfonyl] D-alanine
(3) N [4 (1-hexynyl)phenylsulfonyl] D-alanine
(4) N [4 (1-octynyl)phenylsulfonyl] D-alanine
(5) N [(4-ethynyl)phenylsulfonyl] D-alanine
(6) N [4 (1-propynyl)phenylsulfonyl] D-alanine
(7) N [4 (1-heptynyl)phenylsulfonyl] L-alanine
(8) N [4 (1-pentynyl)phenylsulfonyl] L-alanine
(9) N (4-ethynyl)phenylsulfonyl N-methyl N-benzyl D-glutamine
(10) N (4-ethynyl)phenylsulfonyl N (3-phenylpropyl) D-glutamine
(11) N (4-ethynyl)phenylsulfonyl N (2-phenylethyl) D-glutamine
(12) N (4-ethynyl)phenylsulfonyl N-benzyl D-glutamine
(13) N (4-ethynyl)phenylsulfonyl N (1,2-diphenylethyl) D-glutamine
(14) N (4-ethynyl)phenylsulfonyl N-diphenylmethyl D-glutamine
(15) N (4-ethynyl)phenylsulfonyl N-phenyl D-glutamine
(16) N (4-ethynyl)phenylsulfonyl N (4-methoxyphenyl) D-glutamine
(17) N-methyl N [4 (1-pentynyl)phenylsulfonyl] D-alanine
(18) N-methyl N (4-ethynyl)phenylsulfonyl N-methyl N-phenyl D-glutamine
(19) N-methyl N [4 (1-propynyl)phenylsulfonyl] D-alanine

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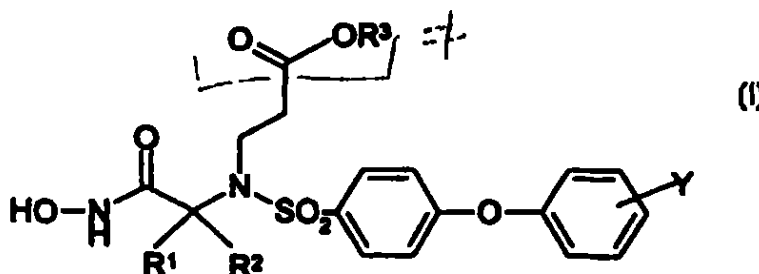
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(54) Title ARYLOXYARYLSULFONYLAMINO HYDROXAMIC ACID DERIVATIVES

(57) Abstract

A compound of formula (I) or the pharmaceutically acceptable salts thereof wherein R¹ is (C₁-C₆)alkyl R² is (C₁-C₆)alkyl or R¹ and R² taken together with the carbon atom to which they are attached form a ring selected from (C₅-C₇)cycloalkyl 4-tetrahydropyranyl and 4-piperidiny R³ is hydrogen or (C₁-C₆)alkyl and Y is a substituent of any of the carbon atoms of the phenyl ring capable of supporting an additional bond

preferably from 1 to 2 substituents (more preferably one substituent most preferably one substituent in the 4-position) on the phenyl ring independently selected from hydrogen fluoro chloro trifluoromethyl (C₁-C₆)alkoxy trifluoromethoxy difluoromethoxy and (C₁-C₆)alkyl

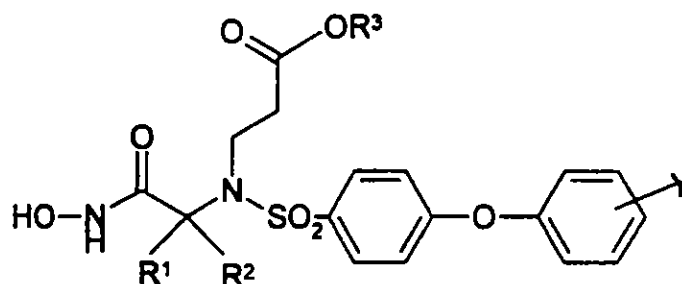


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CLAIMS

1

A compound of the formula



I

or the pharmaceutically acceptable salts thereof wherein

R¹ is (C₁-C₆)alkyl

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R² is (C₁-C₆)alkyl

or R¹ and R² taken together with the carbon atom to which they are attached form a ring selected from (C₅-C₇)cycloalkyl, 4-tetrahydropyranyl and 4-piperidyl

R³ is hydrogen or (C₁-C₆)alkyl and

Y is a substituent on any of the carbon atoms of the phenyl ring capable of supporting an additional bond independently selected from fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, trifluoromethoxy, difluoromethoxy and (C₁-C₆)alkyl

2 A compound according to claim 1 wherein Y is hydrogen, fluoro or chloro

3 A compound according to claim 1 wherein Y is 4-fluoro or 4-chloro

4 A compound according to claim 1 wherein R¹ and R² taken together with the carbon atom to which they are attached form a cyclopentyl ring

5 A compound according to claim 3 wherein R¹ and R² taken together with the carbon atom to which they are attached form a cyclopentyl ring

6 A compound according to claim 1 wherein R¹ and R² taken together with the carbon atom to which they are attached form a 4-tetrahydropyranyl ring

25 7 A compound according to claim 1 wherein R¹ and R² are both methyl

8 A compound according to claim 3 wherein R¹ and R² are both methyl

9 A compound according to claim 1 wherein R³ is hydrogen

10 A compound according to claim 3 wherein R³ is hydrogen

11 A compound according to claim 4 wherein R³ is hydrogen

30 12 A compound according to claim 1 wherein said compound is selected from the group consisting of