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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00066883 00000004 Folios: 2
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Trámite : 002 PATENTES D 1 REGISTRO/ 530 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

E. S. D.

Ref.: Expediente No. 00.066.883.

Solicitud de Patente de Invención Titulada:

"TRATAMIENTO DE COMBINACIÓN CON IL-1RA Y
DIARILSULFONILUREAS QUE INHIBEN EL
PROCESAMIENTO Y LA LIBERACIÓN DE IL-1".

Solicitante: PFIZER PRODUCTS INC.

**SOLICITUD DE EXAMEN DE FONDO SEGÚN EL ARTICULO 44 DE LA
DECISION 486, GACETA No. 519**

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado del solicitante, 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 \$ 318.000 pesos para cubrir la tasa correspondiente, según la Resolución 44691 del año 2001.

Atentamente,



CARLOS R. OLARTE
C.C. No. 79'782.747 de Bogotá
T.P. 74.295

Anexos: Recibo por \$ 318.000 pesos
FTT/P2000/000003 101002.DOC

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NIT : 800176089-2

SUPERINTENDENCIA Y COMERCIO
Radicacion : 00000003 00000004
Fecha (AMD): 2002-10-17 17:49:15

Folios: 2

RECIBO OFICIAL DE CAJA : 02 - 46,969
FECHA : JULIO 18 DE 2002

Tramite : 002 PATENTES A 1 REGISTRO / 530 PETICION
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

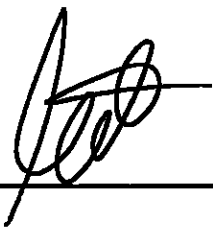
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JULIA ANDRES VARGAS	CONSIGNACION	BANCO POPULAR	050-00110-6	3231623	18/07/2002	18,440,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	998 VALOR COMPLEMENTO TARIFA AND ANTR
			TOTAL : \$ 318,000.00

SON: TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 00-66883

**EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION FUE
PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 519, DE FECHA 29 DE
AGOSTO DE 2002, EL TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL 26 DE
NOVIEMBRE DE 2002.**

**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 caiga 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 _____

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PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



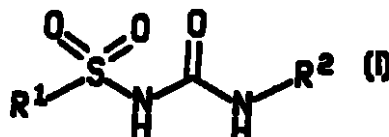
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07C 311/54, A61K 31/64		A1	(11) International Publication Number: WO 98/32733
			(43) International Publication Date: 30 July 1998 (30.07.98)
(21) International Application Number: PCT/IB97/01603		(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, 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, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, 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, 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).	
(22) International Filing Date: 29 December 1997 (29.12.97)		Published With international search report.	
(30) Priority Data: 60/036,979 29 January 1997 (29.01.97) US			
(71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).			
(72) Inventors; and (75) Inventors/Applicants (for US only): DOMBROSKI, Mark, Anthony [US/US]; 36 Stoneheights Drive, Waterford, CT 06385 (US). EGGLER, James, Frederick [US/US]; 184 Elm Street, Stonington, CT 06378 (US).			
(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).			

(54) Title: SULFONYL UREA DERIVATIVES AND THEIR USE IN THE CONTROL OF INTERLEUKIN-1 ACTIVITY

(57) Abstract

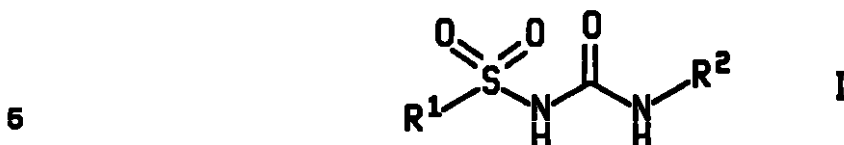
A compound of formula (I) wherein R¹ and R² are as defined in the description, R² being an aromatic group, useful in the treatment and condition selected from the group consisting of the group meningitis and salpingitis, septic shock, disseminated intravascular coagulation, and/or adult respiratory distress syndrome, acute or chronic inflammation, arthritis, cholangitis, colitis, encephalitis, endocarditis, glomerulonephritis, hepatitis, myocarditis, pancreatitis, pericarditis, reperfusion injury, vasculitis, acute and delayed hypersensitivity, graft rejection, and graft-versus-host disease, auto-immune diseases including Type 1 diabetes mellitus and multiple sclerosis, periodonate diseases, interstitial pulmonary fibrosis, cirrhosis, systemic sclerosis, keloid formation tumors which produce IL-1 as an autocrine growth factor, cachexia, Alzheimer's disease, percussion injury, depression, atherosclerosis, osteoporosis in a mammal, including a human.



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CLAIMS

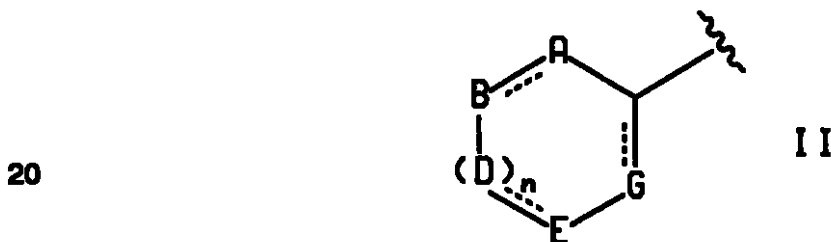
1. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

R¹ is (C₁-C₈)alkyl optionally substituted by (C₁-C₈)alkylamino, (C₁-C₈)alkylthio, (C₁-C₈)alkoxy, trifluoromethyl, (C₆-C₁₀)aryl, (C₆-C₈)heteroaryl, (C₆-C₁₀)arylamino, (C₆-C₁₀)arythio, (C₆-C₁₀)aryloxy, (C₆-C₈)heteroarylamino, (C₆-C₈)heteroarythio, (C₆-C₈)heteroaryloxy, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₃-C₆)cycloalkyl; hydroxy(C₁-C₈)alkyl, (C₁-C₈)alkyl(hydroxymethylene), piperazinyl, (C₆-C₁₀)aryl(C₁-C₈)alkoxy, (C₆-C₈)heteroaryl(C₁-C₈)alkoxy, (C₁-C₈)acylamino, (C₁-C₈)acylthio, (C₁-C₈)acyloxy, (C₁-C₈)alkylsulfinyl, (C₆-C₁₀)arylsulfinyl, (C₁-C₈)alkylsulfonyl, (C₆-C₁₀)arylsulfonyl, amino, (C₁-C₈)alkylamino or
15 ((C₁-C₈)alkyl)₂amino; or

R¹ and R² are each independently a group of the formula



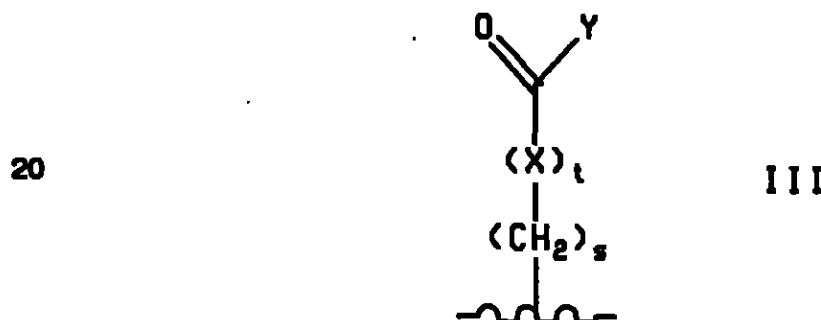
wherein the broken lines represent optional double bonds;

n is 0, 1, 2 or 3;

25 A, B, D, E and G are each independently oxygen, sulfur, nitrogen or CR^aR^b wherein R^a and R^b are each independently selected from hydrogen, (C₁-C₈)alkyl optionally substituted by one or two groups selected from (C₁-C₈)alkylamino, (C₁-C₈)alkylthio, (C₁-C₈)alkoxy, hydroxy, cyano, perfluoro(C₁-C₈)alkyl, (C₆-C₁₀)aryl, (C₆-C₈)heteroaryl, (C₆-C₁₀)arylamino, (C₆-C₁₀)arythio, (C₆-C₁₀)aryloxy wherein the aryl group
30 is optionally substituted by (C₁-C₈)alkoxy, (C₁-C₈)acyl, carboxy, hydroxy or halo; (C₆-C₈)heteroarylamino, (C₆-C₈)heteroarythio, (C₆-C₈)heteroaryloxy, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₃-C₆)cycloalkyl, hydroxy, piperazinyl, (C₆-C₁₀)aryl(C₁-C₈)alkoxy, (C₆-C₈)heteroaryl(C₁-C₈)alkoxy, (C₁-C₈)acylamino, (C₁-C₈)acylthio, (C₁-C₈)acyloxy, (C₁-C₈)alkylsulfinyl, (C₆-

- C_{10})arylsulfinyl, (C_1-C_6) alkylsulfonyl, (C_8-C_{10}) arylsulfonyl, amino, (C_1-C_6) alkylamino or
 $((C_1-C_6)$ alkyl) $_2$ amino; halo, cyano, amino, hydroxy, perfluoro (C_1-C_6) alkyl, perfluoro $(C_1-$
 $C_6)$ alkoxy, (C_2-C_6) alkenyl, carboxy (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_6) alkylamino, $((C_1-$
 $C_6)$ alkyl) $_2$ amino, (C_1-C_6) alkylsulfonylamido, (C_1-C_6) alkylsulfinyl, aminosulfonyl, $(C_1-$
5 $C_6)$ alkylaminosulfonyl, $((C_1-C_6)$ alkyl) $_2$ aminosulfonyl, (C_1-C_6) alkylthio, (C_1-C_6) alkoxy,
perfluoro (C_1-C_6) alkyl, (C_8-C_{10}) aryl, (C_8-C_6) heteroaryl, (C_8-C_{10}) arylamino, (C_8-C_{10}) arylthio,
 (C_8-C_{10}) aryl (C_1-C_6) alkoxy, (C_8-C_6) heteroarylamino, (C_8-C_6) heteroarylthio, $(C_8-$
 $C_6)$ heteroaryloxy, (C_3-C_6) cycloalkyl, (C_1-C_6) alkyl(hydroxymethylene), piperidyl, pyridinyl,
thienyl, furanyl, (C_1-C_6) alkylpiperidyl, (C_1-C_6) acylamino, (C_1-C_6) acylthio, (C_1-C_6) acyloxy,
10 $R^7(C_1-C_6)$ alkyl, wherein R^7 is (C_1-C_6) acylpiperazino, (C_8-C_{10}) arylpiperazino, $(C_8-$
 $C_6)$ heteroarylpiperazino, (C_1-C_6) alkylpiperazino, (C_8-C_{10}) aryl (C_1-C_6) alkylpiperazino, $(C_8-$
 $C_6)$ heteroaryl (C_1-C_6) alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino,
piperidyl, (C_1-C_6) alkylpiperidyl, (C_8-C_{10}) arylpiperidyl, (C_8-C_6) heteroarylpiperidyl, $(C_1-$
 $C_6)$ alkylpiperidyl (C_1-C_6) alkyl, (C_8-C_{10}) arylpiperidyl (C_1-C_6) alkyl, $(C_8-$
15 $C_6)$ heteroarylpiperidyl (C_1-C_6) alkyl or (C_1-C_6) acylpiperidyl;

or a group of the formula



wherein s is 0 to 6;

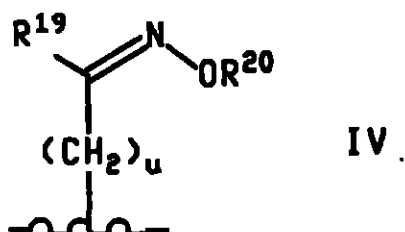
25 t is 0 or 1;

X is oxygen or NR^8 wherein R^8 is hydrogen, (C_1-C_6) alkyl or (C_3-C_7) cycloalkyl $(C_1-$
 $C_6)$ alkyl;

Y is hydrogen, hydroxy, (C_1-C_6) alkyl, optionally substituted by halo, hydroxy or
cyano; (C_1-C_6) alkoxy, cyano, (C_2-C_6) alkynyl, (C_8-C_{10}) aryl wherein the aryl group is
30 optionally substituted by halo, hydroxy, carboxy, (C_1-C_6) alkyl, (C_1-C_6) alkoxy;
perfluoro (C_1-C_6) alkyl, (C_1-C_6) alkoxy (C_1-C_6) alkyl or NR^8R^{10} wherein R^8 and R^{10} are each
independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl optionally
substituted by (C_1-C_6) alkylpiperidyl, (C_8-C_{10}) arylpiperidyl, (C_8-C_6) heteroarylpiperidyl, $(C_8-$

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C_{10})aryl, (C_6-C_8) heteroaryl or (C_3-C_6) cycloalkyl; piperidyl, (C_1-C_6) alkylpiperidyl, (C_6-C_{10}) arylpiperidyl, (C_6-C_8) heteroarylpiperidyl, (C_1-C_6) acylpiperidyl, (C_6-C_{10}) aryl, (C_6-C_8) heteroaryl, (C_3-C_6) cycloalkyl, $R^{11}(C_2-C_6)$ alkyl, (C_1-C_6) alkyl(CHR¹¹)(C₁-C₆)alkyl wherein R¹¹ is hydroxy, (C_1-C_6) acyloxy, (C_1-C_6) alkoxy, piperazino, (C_1-C_6) acylamino, (C_1-C_6) alkylthio, (C_6-C_{10}) arylthio, (C_1-C_6) alkylsulfinyl, (C_6-C_{10}) arylsulfinyl, (C_1-C_6) alkylsulfoxyl, (C_6-C_{10}) arylsulfoxyl, amino, (C_1-C_6) alkylamino, $((C_1-C_6)$ alkyl)₂amino, (C_1-C_6) acylpiperazino, (C_1-C_6) alkylpiperazino, (C_6-C_{10}) aryl(C₁-C₆)alkylpiperazino, (C_6-C_8) heteroaryl(C₁-C₆)alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino; R¹²(C₁-C₆)alkyl, (C_1-C_6) alkyl(CHR¹²)(C₁-C₆)alkyl wherein R¹² is piperidyl or (C_1-C_6) alkylpiperidyl; and CH(R¹³)COR¹⁴ wherein R¹⁴ is as defined below and R¹³ is hydrogen, (C_1-C_6) alkyl, (C_6-C_{10}) aryl(C₁-C₆)alkyl, (C_6-C_8) heteroaryl(C₁-C₆)alkyl, (C_1-C_6) alkylthio(C₁-C₆)alkyl, (C_6-C_{10}) arylthio(C₁-C₆)alkyl, (C_1-C_6) alkylsulfinyl(C₁-C₆)alkyl, (C_6-C_{10}) arylsulfinyl(C₁-C₆)alkyl, (C_1-C_6) alkylsulfonyl(C₁-C₆)alkyl, (C_6-C_{10}) arylsulfonyl(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C_1-C_6) alkylamino(C₁-C₆)alkyl, $((C_1-C_6)$ alkylamino)₂(C₁-C₆)alkyl, R¹⁸R¹⁶NCO(C₁-C₆)alkyl or R¹⁸OCO(C₁-C₆)alkyl wherein R¹⁸ and R¹⁶ are each independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, (C_6-C_{10}) aryl(C₁-C₆)alkyl and (C_6-C_8) heteroaryl(C₁-C₆)alkyl; and R¹⁴ is R¹⁷O or R¹⁷R¹⁶N wherein R¹⁷ and R¹⁶ are each independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, (C_6-C_{10}) aryl(C₁-C₆)alkyl and (C_6-C_8) heteroaryl(C₁-C₆)alkyl; or a group of the formula

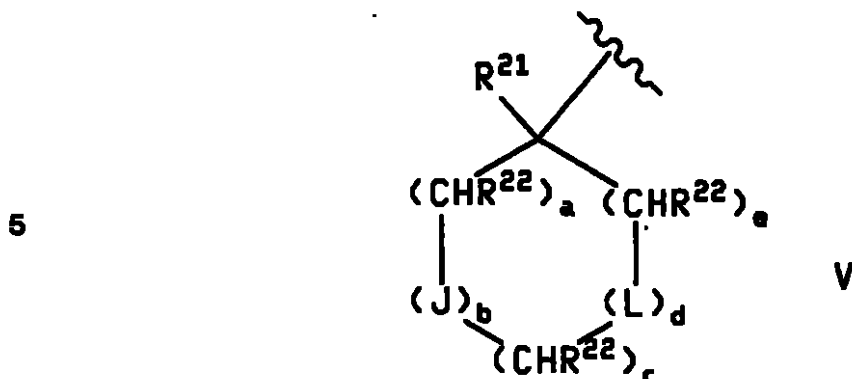


wherein u is 0, 1 or 2;

R¹⁸ is hydrogen, (C_1-C_6) alkyl or perfluoro(C₁-C₆)alkyl;

R²⁰ is hydrogen, (C_1-C_6) alkyl, (C_1-C_6) carboxyalkyl or (C_6-C_{10}) aryl(C₁-C₆)alkyl;

or a group of the formula



10 wherein a is 0, 1 or 2;

b is 0 or 1;

c is 1, 2 or 3;

d is 0 or 1;

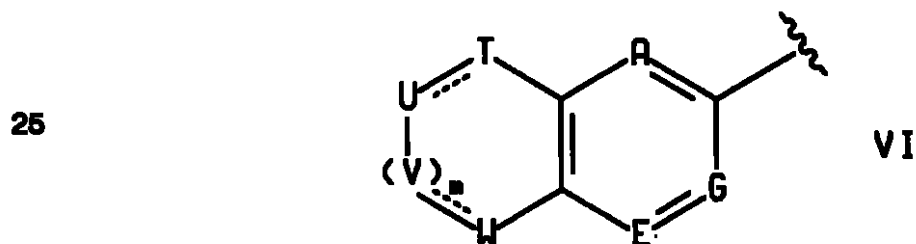
e is 0, 1 or 2;

15 J and L are each independently oxygen or sulfur;

R²¹ is hydrogen, hydroxy, fluoro, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, halo(C₁-C₆)alkyl, amino, (C₁-C₆)acylamino or NR²⁶R²⁷ wherein R²⁶ and R²⁷ are each independently selected from hydrogen, (C₁-C₆)alkyl or (C₆-C₁₀)aryl; and

20 R²² is hydrogen, (C₁-C₆)alkyl optionally substituted by hydroxy, halo, (C₁-C₆)alkylthio, (C₁-C₆)alkylsulfinyl or (C₁-C₆)alkylsulfonyl;

or when n is 1 and B and D are both CR⁵, the two R⁵ groups may be taken together with the carbons to which they are attached to form a group of the formula



wherein the broken lines represent optional double bonds;

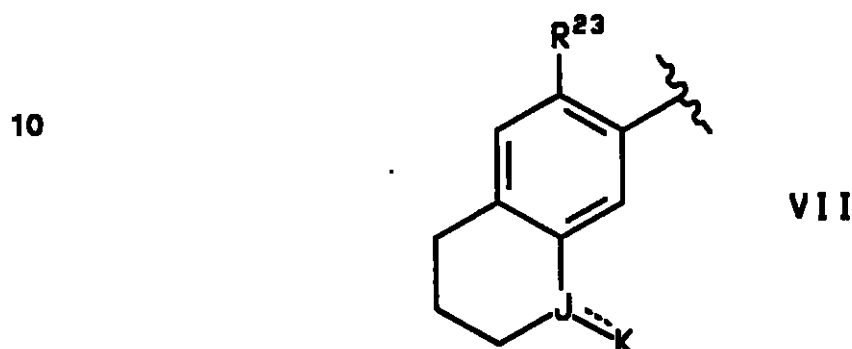
30 m is 0 or 1; and

T, U, V and W are each independently oxygen, sulfur, CO, nitrogen or CR⁵R⁶ wherein R⁵ and R⁶ are as defined above;

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or when A and B, or when n is 1 and B and D, or D and E, or E and G, are both CR^5 , the two R^5 groups may be taken together with the adjacent carbons to which they are attached to form a (C_5-C_8) cycloalkyl group optionally substituted by hydroxy or a benzo group;

5 or when n is 1 and D and E are both CR^5 , the two R^5 groups may be taken together with the adjacent carbons to which they are attached to form a group of the formula



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wherein the broken line represents an optional double bond;

R^{23} is hydrogen, (C_1-C_8) alkyl, halo, amino or (C_1-C_8) alkoxy;

J is C or SO;

20 K is oxygen, NR^{24} wherein R^{24} is hydroxy, (C_1-C_8) alkoxy or (C_6-C_{10}) aryl (C_1-C_8) alkoxy; or hydroxy;

or $R^{25}SO_2$ wherein R^{25} is defined as R^1 above or (C_2-C_7) cycloalkylamino; and

with the proviso that the groups of formulas II and VI cannot have two oxygens, two sulfurs or an oxygen and sulfur defined in adjacent positions;

with the proviso that R^2 must be aromatic;

25 with the proviso that when either a or e is 0, the other must be 1;

with the proviso that when b and d are 1, the sum of a, c and e cannot be 6 or 7; and

with the proviso that when A, B, D, E, G, T, U, V and W represent an sp^2 carbon, R^6 does not exist.

30 2. A compound according to claim 1, wherein R^1 is a group of the formula

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1-(6-Fluoro-1H-benzimidazole-5-sulfonyl)-3-(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)-urea;

1-(4-Chloro-2,6-diisopropyl-phenyl)-3-(1H-Indole-6-sulfonyl)-urea;

1-(4-Chloro-2,6-diisopropyl-phenyl)-3-(5-fluoro-1H-Indole-6-sulfonyl)-urea;

5 1-[1,2,3,5,6,7-Hexahydro-s-Indacen-u-yl)-3-(1H-Indole-6-sulfonyl)-urea;

1-(5-Fluoro-1H-Indole-6-sulfonyl)-3-(1,2,3,5,6,7-hexahydro-5-Indacen-4-yl)-urea;

1-[4-Chloro-2,6-diisopropyl-phenyl]-3-[2-fluoro-5-(2-methyl-(1,3)dioxolan-2-yl)-benzenesulfonyl]-urea;

10 3-[3-[4-Chloro-2,6-diisopropyl-phenyl]-ureldosulfonyl]-N-methyl-benzenesulfonamide;

1-[2-Fluoro-5-(2-methyl-(1,3)dioxolan-2-yl)benzenesulfonyl]-3-1,2,3,5,6,7-hexahydro-Indacen-4-yl)-urea; and

3-[3-(1,2,3,5,6,7-Hexahydro-S-Indacen-4-yl)-ureldosulfonyl]-N-methyl-benzenesulfonamide.

15 6. A pharmaceutical composition for the treatment of meningitis and salpingitis, septic shock, disseminated intravascular coagulation, and/or adult respiratory distress syndrome, acute or chronic inflammation, arthritis, cholangitis, colitis, encephalitis, endocarditis, glomerulonephritis, hepatitis, myocarditis, pancreatitis, pericarditis, reperfusion injury, vasculitis, acute and delayed hypersensitivity, graft
20 rejection, and graft-versus-host disease, auto-immune diseases including Type 1 diabetes mellitus and multiple sclerosis, periodontal diseases, interstitial pulmonary fibrosis, cirrhosis, systemic sclerosis, keloid formation, tumors which produce IL-1 as an autocrine growth factor, cachexia, Alzheimers disease, percussion injury, depression, atherosclerosis and osteoporosis in a mammal, including a human, comprising
25 administering an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in such treatments or inhibition and a pharmaceutically acceptable carrier.

7. A method for treating a condition selected from the group consisting of meningitis and salpingitis, septic shock, disseminated intravascular coagulation, and/or
30 adult respiratory distress syndrome, acute or chronic inflammation, arthritis, cholangitis, colitis, encephalitis, endocarditis, glomerulonephritis, hepatitis, myocarditis, pancreatitis, pericarditis, reperfusion injury, vasculitis, acute and delayed hypersensitivity, graft rejection, and graft-versus-host disease, auto-immune diseases including Type 1

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-75-

diabetes mellitus and multiple sclerosis, periodonate diseases, interstitial pulmonary fibrosis, cirrhosis, systemic sclerosis, keloid formation, tumors which produce IL-1 as an autocrine growth factor, cachexia, Alzheimers disease, percussion injury, depression, atherosclerosis and osteoporosis in a mammal, including a human, comprising
5 administering to said mammal an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in treating such a condition.

8. The compound 4-(1-hydroxy-1-methyl-ethyl)-furan-2-sulfonamide.

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US005874424A

United States Patent [19]

Batchelor et al.

[11] Patent Number: 5,874,424

[45] Date of Patent: Feb. 23, 1999

[54] INHIBITORS OF INTERLEUKIN-1 β CONVERTING ENZYME

[75] Inventors: Mark James Batchelor, Cumnor Hill; David Bebbington, Pewsey, both of United Kingdom; Guy W. Bemis, Arlington, Mass.; Wolf Herman Fridman, Paris, France; Roger John Gillespie, Oaksey; Julian M. C. Golec, Ashbury, both of United Kingdom; David J. Lauffer, Stow; David J. Livingston, Newtonville, both of Mass.; Saroop Singh Matharu, Cricklade, United Kingdom; Michael D. Mullican, Needham; Mark A. Mureko, Holliston, both of Mass.; Robert Murdoch, Highworth, United Kingdom; Robert E. Zelle, Stow, Mass.

[73] Assignee: Vertex Pharmaceuticals Incorporated, Cambridge, Mass.

[21] Appl. No.: 598,332

[22] Filed: Feb. 8, 1996

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 575,641, Dec. 20, 1995.

[51] Int. Cl.⁶ A61K 31/55; C07D 243/02

[52] U.S. Cl. 514/221; 514/211; 514/220; 540/491; 540/495; 540/500; 540/501

[58] Field of Search 540/500; 514/221

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Attorney, Agent, or Firm—Fish & Neave; James F. Haley, Jr.; Lisa A. Dixon

[57] ABSTRACT

The present invention relates to novel classes of compounds which are inhibitors of interleukin-1 β converting enzyme. The ICE inhibitors of this invention are characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently, may be advantageously used as agents against an IL-1 mediated disease, an apoptosis mediated disease, AML, CML, melanoma, myeloma, Kaposi's sarcoma, graft vs host disease, rheumatoid arthritis, inflammatory bowel disorder, psoriasis, osteoarthritis, myeloma, apoptosis, sepsis, rheumatoid arthritis, asthma, Alzheimer's disease, Parkinson's disease, and ischemic heart disease diseases. This invention also relates to methods for inhibiting ICE activity and methods for treating interleukin-1 mediated diseases using the compounds and compositions of this invention.

7 Claims, 33 Drawing Sheets

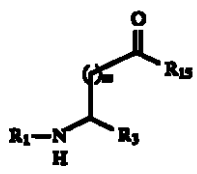
301

to mammals, they are of evident clinical utility for the treatment of IL-1- and apoptosis-mediated diseases. These tests are predictive of the compounds ability to inhibit ICE in vivo.

While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the products and processes of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific embodiments which have been presented by way of example.

We claim:

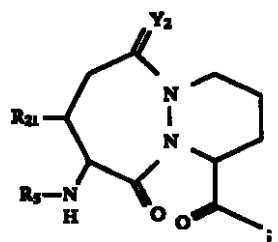
1. A compound represented by the formula:



wherein:

m is 1 or 2;

R₁ is:



R₃ is selected from the group consisting of:

- CN,
- C(O)—H,
- C(O)—CH₂—T₁—R₁₁,
- C(O)—CH₂—R_i,
- C—N—O—R_p, and
- CO—Ar₂;

each R₅ is independently selected from the group consisting of:

- C(O)—R₁₀,
- C(O)O—R_p,
- C(O)—N(R₁₀)(R₁₀)
- S(O)₂—R_p,
- S(O)₂—NH—R₁₀,
- C(O)—CH₂—O—R_p,
- C(O)C(O)—R₁₀,
- R_p,
- H,
- C(O)C(O)—OR₁₀, and
- C(O)C(O)—N(R₉)(R₁₀);

Y₂ is H₂ or O;

each T₁ is independently selected from the group consisting of —O—, —S—, —S(O)—, and —S(O)₂—;

each R₉ is independently selected from the group consisting of —Ar₃ and a —C₁₋₆ straight or branched alkyl group optionally substituted with Ar₃, wherein the —C₁₋₆ alkyl group is optionally an unsaturated —C₂₋₆ alkenyl group;

each R₁₀ is independently selected from the group consisting of —H, —Ar₃, a C₂₋₆ cycloalkyl group, and a —C₁₋₆ straight or branched alkyl group optionally

302

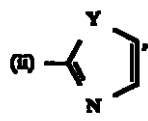
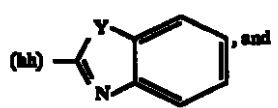
substituted with Ar₃, wherein the —C₁₋₆ alkyl group is optionally an unsaturated —C₂₋₆ alkenyl group; each R₁₁ is independently selected from the group consisting of:

- Ar₄,
- (CH₂)₁₋₅—Ar₄,
- H, and
- C(O)—Ar₄;

R₁₅ is selected from the group consisting of —OH, —OAr₃, —N(H)—OH, and —OC₁₋₆, wherein C₁₋₆ is a straight or branched alkyl group optionally substituted with Ar₃, —CONH₂, —OR₃, —OH, —OR₉, or —CO₂H;

R₂₁ is —CH₃;

Ar₂ is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by —Q₁ or phenyl, optionally substituted by Q₁:



wherein each Y is independently selected from the group consisting of O and S;

each Ar₃ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group selected from the group consisting of pyrimidinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, purinyl, pyrimidyl, indolyl, benzimidazolyl, imidazolyl, imidazolinoyl, quinolyl, isoquinolyl, indolyl, pyridyl, pyrrolyl, pyrazolyl, pyrazinyl, quinoxolyl, furyl, thienyl, triazolyl, thiazolyl, β-carbolinyl, tetrazolyl, benzofuranyl, benzoxazolyl, isoxazolyl, thiadiazolyl, benzodioxolyl, benzothienyl, naphthyridinyl, pyridazinyl, phthalazinyl, pyridodiazinyl, triazinyl, thienothiophenyl, thienopyridinyl, oxadiazolyl, benzothiazolyl, benzotriazolyl, isoxazolopyridinyl, isothiazolyl, benzoisoxazolyl, benzoisothiazolyl, isothiazopyridyl, benzothiazolyl, benzofuranyl, carbazolyl, phenothiazinyl, phenanthridinyl, acridinyl, dibenzothiophenyl, oxazole, indoliziny, isoindolyl, indazolyl, quinoliziny, cinnoliny, quinazolinyl, pteridinyl, phenazinyl, and phenoxazinyl, and said cyclic group optionally being singly or multiply substituted by —Q₁;

each Ar₄ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group selected from the group consisting of pyrimidinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, purinyl, pyrimidyl, indolyl, benzimidazolyl, imidazolyl, imidazolinoyl, indazolidiny, quinolyl, isoquinolyl, indolyl, pyridyl, pyrrolyl, pyrrolinyl, pyrazolyl, pyrazinyl, quinoxolyl, piperidinyl, morpholinyl, thiamorpholinyl, furyl, thienyl, triazolyl, thiazolyl, β-carbolinyl, tetrazolyl, thiazolidinyl, benzofuranyl, thiamorpholinyl sulfone, benzoxazolyl, oxopiperidinyl, oxopyrrolidinyl,

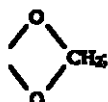
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oxazepinyl, azepinyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuranyl, thiadiazolyl, benzodioxolyl, benzothienyl, tetrahydrothiophenyl, naphthyridinyl, pyridazinyl, phthalazinyl, pyridodiazinyl, triazinyl, thienothiophenyl, thienopyridinyl, oxadiazolyl, benzothiazolyl, benzotriazolyl, isoxazolopyridinyl, isothiazolyl, benzoisoxazolyl, benzoisothiazoyl, isothiazopyridyl, benzothiazolyl, benzofuranyl, carbazolyl, phenothiazinyl, phenanthridinyl, acridinyl, dibenzothiophenyl, pyranyl, thiopyranyl, oxazinyl, thiazinyl, oxadiazinyl, thiadiazinyl, pyrrolidinyl, oxepanyl, theipanyl, diazepinyl, thiazepinyl, diazepanyl, oxazepanyl, thiazepanyl, pyrazolidinyl, oxazole, indolizinyl, isoindolyl, indazolyl, quinolizinyl, cinnolinyl, quinazolinyl, pteridinyl, phenazinyl, and phenoxazinyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $=O$, $-OH$, perfluoro C_{1-3} alkyl, R_2 , $-OR_2$, $-NHR_2$, OR_2 , $-N(R_2)$ (R_{10}), R_9 , $-C(O)-R_{10}$, and

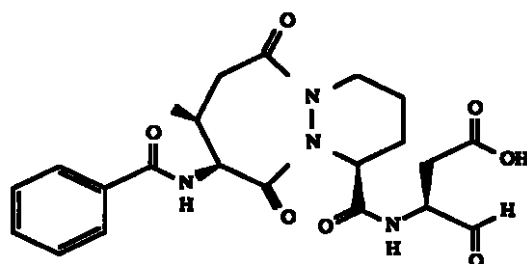


provided that when $-Ar_2$ is substituted with a Q_1 group which comprises one or more additional $-Ar_2$ groups, said additional $-Ar_2$ groups are not substituted with another $-Ar_2$.

2. The compound according to claim 1, wherein R_2 is $-C(O)-H$.

3. The compound according to claim 2, wherein the compound is:

304



257

4. A pharmaceutical composition for treating an IL-1 mediated or an apoptosis mediated disease comprising a therapeutically effective amount of a compound according to claim 1, 2, or 3 and a pharmaceutically acceptable carrier.

5. A pharmaceutical composition for treating a disease selected from osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, graft vs. host disease, septic shock, cerebral ischemia and neurological damage due to stroke comprising a therapeutically effective amount of a compound according to claim 1, 2 or 3 and a pharmaceutically acceptable carrier.

6. A method for treating an IL-1 mediated or an apoptosis mediated disease comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to claim 1, 2 or 3.

7. A method for treating a disease selected from osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, graft vs. host disease, septic shock, cerebral ischemia and neurological damage due to stroke comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to claim 1, 2 or 3.

* * * * *

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US98/20465 (22) International Filing Date: 30 September 1998 (30.09.98) (30) Priority Data: 08/944,479 6 October 1997 (06.10.97) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 08/944,479 (CIP) Filed on 6 October 1997 (06.10.97) (71) Applicant (for all designated States except US): BASF AK-TIENGESSELLSCHAFT [DE/DE]; Carl-Bosch-Strasse 38, D-67056 Ludwigshafen (DE). (72) Inventors; and (75) Inventors/Applicants (for US only): BARLOZZARI, Teresa [IT/US]; 24 South Woodside Avenue, Wellesley, MA 02181 (US). BANERJEE, Subhashis [IN/US]; 35 Hapgood Way, Shrewsbury, MA 01545 (US). HAUPT, Andreas [DE/US]; 33 Catherine Drive, Northborough, MA 01532 (US).		(74) Agents: GRANAHAN, Patricia et al.; Hamilton, Brook, Smith & Reynolds, P.C., Two Militia Drive, Lexington, MA 02421 (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, HR, 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, US, 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). Published <i>Without international search report and to be republished upon receipt of that report.</i>	
(54) Title: METHODS AND COMPOSITIONS FOR TREATING RHEUMATOID ARTHRITIS			
(57) Abstract The present invention provides compositions and methods for the treatment of rheumatoid arthritis in a subject wherein one or more compounds of Formula (I) as defined herein alone or in combination with one or more other antiarthritic drugs provide suppression of rheumatoid arthritis.			

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-3-

methylcyclohexyl; or a C₁-C₁₂ linear or branched alkyl group, such as

-C(CH₃)₃, also referred to as tert-butyl;

5 -C(CH₃)₂-CH₂-CH₃, also referred to as 1,1-dimethylpropyl;

-C(CH₃)(CH₂-CH₃)₂, also referred to as 1-methyl-1-ethylpropyl;

10 -CH(CH₃)-C(CH₃)₂, also referred to as (S)- or (R)-1-methyl-2,2-dimethyl-propyl;

-CH(CH₃)-CH(CH₃)₂, also referred to as (S)- or (R)-1-ethyl-2-methylpropyl;

-CH(CH₃)-CH(CH₃)₂, also referred to as 1-isopropyl-2-methyl-propyl; or

15 -C(CH₃)₂-CH(CH₃)₂, also referred to as 1,1-dimethyl-2-methylpropyl;

-CH(CH₃)₂, also referred to as isopropyl;

-CH(CH₃)CH₂CH₂CH₃, sec-butyl [(S) or (R)]; or

-CH(CH₃)CH(CH₃)₂, also referred to as 1,2-dimethylpropyl.

20 This invention also relates to methods for the treatment of rheumatoid arthritis, in a mammal, for example a human, in which one or more of the Dolastatin-15 derivatives described herein are used. In the method of the present invention, one or more of the Dolastatin-15
25 derivatives are administered, alone or in a pharmacologically acceptable carrier, in a therapeutically effective amount to treat rheumatoid arthritis in a mammal having or susceptible to rheumatoid arthritis.

In another aspect of the invention one or more
30 Dolastatin-15 derivatives are administered in combination with one or more other antiarthritic drugs to a mammal having or susceptible to rheumatoid arthritis.

In a specific embodiment, two or more Dolastatin-15 derivatives are administered alone or in combination with

-4-

one or more other antiarthritic drugs to a mammal having or susceptible to rheumatoid arthritis. Administration of two or more Dolastatin-15 derivatives or administration of Dolastatin-15 derivative(s) in combination with one or more other antiarthritic drugs enhances treatment of rheumatoid arthritis: For example, a combination provides a greater suppression or fewer side effects, and/or can make it possible to administer a lower dose of the known antiarthritic drug to produce the same effect produced with a higher dose. The other antiarthritic drug can be, but is not limited to, one or more of the following: (1) a nonsteroidal anti-inflammatory agent such acetylsalicylic (aspirin), ibuprofen, or naproxen; (2) an organic gold derivative such a gold sodium thiomalate, aurothioglucose, or auranofin; (3) D-pencillamine; (4) a 4-aminoquinoline agent such as hydroxychloroquine; (5) azathioprine; (6) methotrexate; (7) cyclosporin; (8) an angiogenesis inhibitor such as AGM-1470 (Ingber, et al., Nature 348, (1990) 555); (9) monoclonal antibodies to T cells; (10) monoclonal antibodies to adhesion molecules; (11) monoclonal antibodies to cytokines and growth factors; (12) Tumor Necrosis Factor Receptor (TNFR)-IgG ; (13) IL-1 receptor antagonists; and (14) ICE inhibitors.

Also the subject of this invention are pharmaceutical compositions which comprise one or more Dolastatin-15 derivatives of Formula I either alone or in combination with one or more other antiarthritic drugs. The pharmaceutical composition can optionally include a pharmaceutically acceptable carrier, diluent or a compound which aids in processing, for example, binders, fillers and preservatives.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts compounds i-xvii, as examples of Dolastatin-15 derivatives having the structure of Formula I.

853
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-81-

CLAIMS

What is claimed is:

1. A method for the treatment of rheumatoid arthritis in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of Formula I:



wherein:

R^1 is alkyl, cycloalkyl, alkylsulfonyl, fluoroalkyl, or aminosulfonyl;

R^2 is hydrogen, alkyl, fluoroalkyl or cycloalkyl;

R^1-N-R^2 together may be a pyrrolidino or piperidino residue;

A is a valyl, isoleucyl, leucyl, allo-isoleucyl, 2,2-dimethylglycyl, 2-cyclopropylglycyl, 2-cyclopentylglycyl, 3-tert-butylalanyl, 2-tert-butylglycyl, 3-cyclohexylalanyl, 2-ethylglycyl, 2-cyclohexylglycyl, norleucyl or norvalyl residue;

B is a N-alkyl-valyl, -norvalyl, -leucyl, -isoleucyl, -2-tert-butylglycyl, -3-tert-butylalanyl, -2-ethylglycyl, -2-cyclopropylglycyl, -2-cyclopentylglycyl, norleucyl or -2-cyclohexylglycyl residue;

-82-

- 5 D is a prolyl, homoprolyl, hydroxyprolyl, 3,4-dehydroprolyl, 4-fluoroprolyl, 3-methylprolyl, 4-methylprolyl, 5-methylprolyl, azetidine-2-carbonyl, 3,3-dimethylprolyl, 4,4-difluoroprolyl, oxazolidine-4-carbonyl or thiazolidine-4-carbonyl residue;
- 10 E is a prolyl, homoprolyl, hydroxyprolyl, 3,4-dehydroprolyl, 4-fluoroprolyl, 3-methylprolyl, 4-methyl prolyl, 5-methylprolyl, azetidine-2-carbonyl, 3,3-dimethylprolyl, 4,4-difluoroprolyl, oxazolidine-4-carbonyl or thiazolidine-4-carbonyl residue;
- 15 F and G are independently selected from the group consisting of prolyl, homoprolyl, hydroxyprolyl, thiazolidinyl-4-carbonyl, 1-aminopentyl-1-carbonyl, valyl, 2-tert-butylglycyl, isoleucyl, leucyl, 3-cyclohexylalanyl, phenylalanyl, N-methylphenylalanyl, tetrahydroisoquinolyl-2-histidyl, 1-aminoindyl-1-carbonyl, 3-pyridylalanyl, 2-cyclohexylglycyl, norleucyl, norvalyl, neopentylglycyl, tryptophanyl, glycyl, 2,2-dimethylglycyl, alanyl, β -alanyl
- 20 and 3-naphthylalanyl residues;
- 25 X is hydrogen, alkyl, cycloalkyl, $-\text{CH}_2-$ cyclohexyl or arylalkyl;
- s, t and u are independently 0 or 1; and
- 30 K is hydroxy, alkoxy, phenoxy, benzyloxy or a substituted or unsubstituted amino moiety;

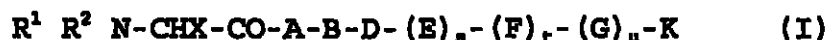
-96-

hydrogen or C₁-C₄ alkoxy and R⁶ is a C₃₋₁₀ cycloalkyl selected from the group consisting of: (1)-adamantyl, (2)-adamantyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclopentyl, 1-methylcyclohexyl and [3.3.0]octa-1-yl.

23. An invention of Claim 17 wherein for the compound of Formula I R¹ and R² are each methyl; X is isopropyl; s is 1; t and u are each 0; A is valyl; B is N-methylvalyl; D is prolyl; E is prolyl; R⁵ is hydrogen and R⁶ is tert-butyl.

24. An invention of Claim 17 wherein for the compound of Formula I R¹ and R² are each methyl; X is isopropyl; s is 1; t and u are each 0; A is valyl; B is N-methylvalyl; D is prolyl; E is prolyl; R⁵ is benzyl and R⁶ is hydrogen.

25. A pharmaceutical composition comprising:
a) a therapeutically effective amount of a compound of Formula I:



20 wherein:

R¹ is alkyl, cycloalkyl, alkylsulfonyl, fluoroalkyl, or aminosulfonyl;

R² is hydrogen, alkyl, fluoroalkyl or cycloalkyl;

25 R¹-N-R² together may be a pyrrolidino or piperidino residue;

A is a valyl, isoleucyl, leucyl, allo-isoleucyl, 2,2-dimethylglycyl, 2-cyclopropylglycyl, 2-cyclopentylglycyl, 3-tert-butylalanyl, 2-tert-

856
544

-97-

butylglycyl, 3-cyclohexylalanyl, 2-ethylglycyl, 2-cyclohexylglycyl, norleucyl or norvalyl residue;

- 5 B is a N-alkyl-valyl, -norvalyl, -leucyl, -isoleucyl, -2-tert-butylglycyl, -3-tert-butylalanyl, -2-ethylglycyl, -2-cyclopropylglycyl, -2-cyclopentylglycyl, norleucyl or -2-cyclohexylglycyl residue;
- 10 D is a prolyl, homoprolyl, hydroxyprolyl, 3,4-dehydroprolyl, 4-fluoroprolyl, 3-methylprolyl, 4-methylprolyl, 5-methylprolyl, azetidine-2-carbonyl, 3,3-dimethylprolyl, 4,4-difluoroprolyl, oxazolidine-4-carbonyl or thiazolidine-4-carbonyl residue;
- 15 E is a prolyl, homoprolyl, hydroxyprolyl, 3,4-dehydroprolyl, 4-fluoroprolyl, 3-methylprolyl, 4-methyl prolyl, 5-methylprolyl, azetidine-2-carbonyl, 3,3-dimethylprolyl, 4,4-difluoroprolyl, oxazolidine-4-carbonyl or
- 20 thiazolidine-4-carbonyl residue;
- 25 F and G are independently selected from the group consisting of prolyl, homoprolyl, hydroxyprolyl, thiazolidinyl-4-carbonyl, 1-aminopentyl-1-carbonyl, valyl, 2-tert-butylglycyl, isoleucyl, leucyl, 3-cyclohexylalanyl, phenylalanyl, N-methylphenylalanyl, tetrahydrosioquinolyl-2-histidyl, 1-aminoindyl-1-carbonyl, 3-pyridylalanyl, 2-cyclohexylglycyl, norleucyl,
- 30 norvalyl, neopentylglycyl, tryptophanyl, glycyl, 2,2-dimethylglycyl, alanyl, β -alanyl

357
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-98-

and 3-naphthylalanyl residues;

X is hydrogen, alkyl, cycloalkyl, -CH₂-
cyclohexyl or arylalkyl;

s, t and u are independently 0 or 1; and

5 K is hydroxy, alkoxy, phenoxy, benzyloxy or a
substituted or unsubstituted amino moiety;

and the salts thereof with physiologically tolerated
acids; and

10 b) a therapeutically effective amount of a second
antiarthritic drug selected from the group
consisting of: a nonsteroidal antiinflammatory
agent, an organic gold derivative, D-
penicillamine, a 4-aminoquinoline, azathioprine,
15 methotrexate, cyclosporin, an angiogenesis
inhibitor, a monoclonal antibody to T cells, a
monoclonal antibody to an adhesion molecule, a
monoclonal antibody to a cytokine or growth
factor, TNFR-IgG, IL-1 receptor antagonists and
20 ICE inhibitors.

26. The composition of Claim 25 wherein the compound has
the formula as defined in any one of claims 14-24.

27. The composition of Claim 25 or 26 for use in therapy
or prophylaxis, for example, in the treatment of
25 rheumatoid arthritis in a mammal (e.g., a human).

558
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US98/19841			(74) Agents: GRANAHAN, Patricia et al.; Hamilton, Brook, Smith & Reynolds, P.C., Two Militia Drive, Lexington, MA 02421 (US).
(22) International Filing Date: 24 September 1998 (24.09.98)			
(30) Priority Data: 08/944,479 6 October 1997 (06.10.97) US			
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 08/944,479 (CIP) Filed on 6 October 1997 (06.10.97)			
(71) Applicant (for all designated States except US): BASF AKTIENGESELLSCHAFT [DE/DE]; Carl-Bosch-Strasse 38, D-67056 Ludwigshafen (DE).			
(72) Inventors; and (75) Inventors/Applicants (for US only): BARLOZZARI, Teresa [IT/US]; 24 South Woodside Avenue, Welleale, MA 02181 (US). BANERJEE, Subhashis [IN/US]; 35 Hapgood Way, Shrewsbury, MA 01545 (US). HAUPT, Andreas [DE/US]; 33 Catherine Drive, Northborough, MA 01532 (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, GH, GM, HR, 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, US, 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).
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: METHODS AND COMPOSITIONS FOR TREATING RHEUMATOID ARTHRITIS			
(57) Abstract The present invention provides compositions and methods for the treatment of rheumatoid arthritis in a subject wherein one or more compounds of Formula (I) as defined herein alone or in combination with one or more other antiarthritic drugs provide suppression of rheumatoid arthritis.			

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-3-

- methyleyclohexyl; or a C₁-C₁₂ linear or branched alkyl group, such as
- C(CH₃)₃, also referred to as tert-butyl;
 - 5 -C(CH₃)₂-CH₂-CH₃, also referred to as 1,1-dimethylpropyl;
 - C(CH₃)(CH₂-CH₃)₂, also referred to as 1-methyl-1-ethylpropyl;
 - 10 -CH(CH₃)-C(CH₃)₂, also referred to as (S)- or (R)-1-methyl-2,2-dimethyl-propyl;
 - CH(CH₃)-CH(CH₃)₂, also referred to as (S)- or (R)-1-ethyl-2-methylpropyl;
 - CH(CH₃)-CH(CH₃)₂, also referred to as 1-isopropyl-2-methyl-propyl; or
 - 15 -C(CH₃)₂-CH(CH₃)₂, also referred to as 1,1-dimethyl-2-methylpropyl;
 - CH(CH₃)₂, also referred to as isopropyl;
 - CH(CH₃)CH₂CH₃, sec-butyl [(S) or (R)]; or
 - 20 -CH(CH₃)CH(CH₃)₂, also referred to as 1,2-dimethylpropyl.

This invention also relates to methods for the treatment of rheumatoid arthritis, in a mammal, for example a human, in which one or more of the Dolastatin-15 derivatives described herein are used. In the method of

25 the present invention, one or more of the Dolastatin-15 derivatives are administered, alone or in a pharmacologically acceptable carrier, in a therapeutically effective amount to treat rheumatoid arthritis in a mammal having or susceptible to rheumatoid arthritis.

30 In another aspect of the invention one or more Dolastatin-15 derivatives are administered in combination with one or more other antiarthritic drugs to a mammal having or susceptible to rheumatoid arthritis.

In a specific embodiment, two or more Dolastatin-15

35 derivatives are administered alone or in combination with

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one or more other antiarthritic drugs to a mammal having r
susceptible to rheumatoid arthritis. Administration of two
or more Dolastatin-15 derivatives or administration of
Dolastatin-15 derivative(s) in combination with one or more
5 other antiarthritic drugs enhances treatment of rheumat id
arthritis. For example, a combination provides a greater
suppression or fewer side effects, and/or can make it
possible to administer a lower dose of the known
antiarthritic drug to produce the same effect produced
10 with a higher dose. The other antiarthritic drug can be,
but is not limited to, one or more of the following: (1) a
nonsteroidal anti-inflammatory agent such acetylsalicylic
(aspirin), ibuprofen, or naproxen; (2) an organic gold
derivative such a gold sodium thiomalate, aurothioglucose,
15 or auranofin; (3) D-pencillamine; (4) a 4-aminoquinoline
agent such as hydroxychloroquine; (5) azathioprine; (6)
methotrexate; (7) cyclosporin; (8) an angiogenesis
inhibitor such as AGM-1470 (Ingber, et al., Nature 348,
(1990) 555); (9) monoclonal antibodies to T cells; (10)
20 monoclonal antibodies to adhesion molecules; (11)
monoclonal antibodies to cytokines and growth factors; (12)
Tumor Necrosis Factor Receptor (TNFR)-IgG ; (13) IL-1
receptor antagonists; and (14) ICE inhibitors.

Also the subject of this invention are pharmaceutical
25 compositions which comprise one or more Dolastatin-15
derivatives of Formula I either alone or in combination
with one or more other antiarthritic drugs. The
pharmaceutical composition can optionally include a
pharmaceutically acceptable carrier, diluent or a compound
30 which aids in processing, for example, binders, fillers and
preservatives.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts compounds i-xvii, as examples of
Dolastatin-15 derivatives having the structure of Formula
35 I.

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561

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

2020
Bogotá, D.C.,

Doctor
CARLOS R. OLARTE
(Apoderado)

ASUNTO	Radicación	00066883
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	9020
	Folios	028

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:

Documentos estudiados:

Los textos estudiados fueron la descripción (Folios: 327 a 468) y las reivindicaciones 1 a 15 (Folios: 469 a 486).

La presente solicitud reivindica prioridad americana N° US60.154010 de 14 de septiembre de 1999 y cumple con lo establecido en los artículos 9, 10 y 11 de la Decisión 486 de la Comisión de la Comunidad Andina.

Objeto de Invención:

La presente solicitud se titula: "Tratamiento de combinación con IL-1ra y compuestos que inhiben el procesamiento y la liberación de IL-1".

El objeto de la presente solicitud se refiere a métodos y composiciones para el tratamiento de estados morbosos mediados por IL-1, que comprende administrar conjuntamente, a un animal mamífero que necesite dicho tratamiento, cantidades eficaces de un polipéptido IL-1ra o de una variante del mismo, y de un agente no esteroide que inhibe el procesamiento y la liberación de IL-1. La solicitud además proporciona composiciones que comprenden un polipéptido IL-1ra o una variante del mismo, y un agente no esteroide que inhibe el procesamiento y la liberación de IL-1. El metotrexato, la leflunomida y similares no son agentes inhibidores del procesamiento y la liberación de IL-1 pero pueden influir en el eje de IL-1 porque de ellos se sabe que ejercen sus efectos por medio de una supresión de la división celular. Cuando se suprime la división celular, puede reducirse el número de células disponibles para producir citoquinas y, por tanto, puede reducirse la cantidad de IL-1 en el sistema.

Según la descripción, la interleuquina 1 se refiere a dos proteínas (IL-1 alfa e IL-1 beta, también denominadas IL-1 a e IL-1 b, respectivamente) que desempeñan una función clave temprana en la respuesta inflamatoria. Ambas proteínas son generadas como proteínas precursoras intracelulares de 31 kDa que son escindidas y secretadas para

producir fragmentos carboxi-terminales maduros de 17 kDa que son biológicamente activos. En el caso de Il-1beta, esta escisión implica a una cisteína proteasa intracelular, conocida como ICE que es necesaria para que se libere el fragmento activo a partir del precursor inactivo. El precursor de Il-1alfa es activo.

Estas dos proteínas actúan uniéndose a receptores de la superficie celular presentes en casi todos los tipos celulares y desencadenando una variedad de respuestas, solas o junto con otros factores secretados. Estas respuestas incluyen efectos sobre la proliferación, apoptosis, inducción de citoquinas, activación de receptores, producción de compuestos eicosanoides y secreción de enzimas degradantes. Para alcanzar esto, la Il-1 activa factores de transcripción tales como NF-kB y AP-1. Se cree que varias de las actividades de la acción de Il-1 sobre células diana son mediadas por la activación de cascadas de quinasas que han sido también asociadas con estreses celulares, tales como las quinasas JNK/SAPK y p38 de MAP activadas por estrés.

De acuerdo con la presente solicitud, en diversas patentes y publicaciones como las detalladas más adelante se han descrito terapias que implican la administración de proteínas Il-1ra y un agente inhibidor del procesamiento y la liberación de Il-1. Se ha descubierto ahora que la combinación de un polipéptido Il-1ra y un agente inhibidor del procesamiento y la liberación de Il-1 del presente invento proporciona un beneficio sinérgico con respecto a los agentes individuales solos. Por lo tanto, las combinaciones del presente invento permiten dosis terapéuticas eficaces de un Il-1ra que están significativamente reducidas en comparación con las que se requieren en ausencia del agente inhibidor del procesamiento y la liberación de Il-1, y la combinación es además significativamente más eficaz que lo es la administración de un agente inhibidor del procesamiento y la liberación de Il-1 solo o que el agente inhibidor del procesamiento y la liberación de Il-1 solo.

Lo que se reivindica como novedoso es lo siguiente: un método para tratar o prevenir estados morbosos mediados por Il-1, que comprende administrar conjuntamente a un animal mamífero que necesite dicho tratamiento, cantidades eficaces de un polipéptido Il-1ra o de una variante del mismo, y de un agente no esteroide que inhibe el procesamiento y la liberación de Il-1.

También reivindica: una composición que comprende un polipéptido Il-1ra o una variante del mismo, y un agente no esteroide que inhibe el procesamiento y la liberación de Il-1.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/18, 31/17.

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 10 (folio: 478) y sus dependientes no son claras toda vez que son muy generales y especulativas, ya que no se dice en

forma clara a cuál polipéptido se refiere ni a cuál agente esteroide que son los componentes de la composición farmacéutica de que tratan tales reivindicaciones. Asimismo, no se dice cuál es el vehículo de dicha composición ni las cantidades en que van por lo menos los principios activos.

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, de los animales, o para la preservación de los vegetales o del medio ambiente sólo 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): 1 a 9 (Folios: 469 a 478), que se refiere(n) a un método para tratar o prevenir estados morbosos mediados por IL-1, no es (son) patentable(s).

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."

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".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 14/09/1999, 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 anterioridades (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	Título	Fecha de Publicación
1	WO 98/32733	Sulfonyl urea derivatives and their use in the control of interleukin-1 activity	30 de Julio de 1998
2	US 5874424	Inhibitors of interleukin-1 β converting enzyme	23 de febrero de 1999
3	WO 99/17709	Methods and compositions for treating rheumatoid arthritis	15 de abril de 1999
4	WO 99/17792	Methods and compositions for treating rheumatoid arthritis	15 de abril de 1999

Evaluación de los requisitos de Patentabilidad:

El Artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina el cual 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".

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 Nivel Inventivo:

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "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".

El Nivel Inventivo se evaluó por comparación entre lo solicitado y encontrado en el estado de la técnica y que se relaciona con el objeto reivindicado y de acuerdo con la definición de nivel inventivo del Artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina.

La Solicitud de Patente Colombiana No. 00066883, se refiere a:

Una composición que comprende un polipéptido IL-1ra o una variante del mismo, y un agente no esteroide que inhibe el procesamiento y la liberación de IL-1.

La anterioridad: WO 98/32733 (follos: 539 a 546), se relaciona con: derivados de sulfonil úrea dentro de los cuales está el compuesto de fórmula I derivado de diarilsulfonilúrea que forma parte de la composición de la reivindicación 12 (ver follos: 478 a 483) y tiene actividad antiinflamatoria. Además, se habla en este documento de composiciones farmacéuticas que los contienen.

La anterioridad: US 5874424 (folios: 547 a 549), trata sobre: Inhibidores de enzima convertidora de Interleukina 1beta (ICE) y que se utiliza para el tratamiento de apoptosis, osteoartritis, asma, artritis reumatoidea, etc.

El documento WO 99/17709 (folios: 550 a 557) menciona métodos y composiciones para tratar la artritis reumatoidea. En especial menciona composiciones que contienen dos agentes que tienen propiedades contra la artritis.

El documento WO 99/17792 (follos: 558 a 560) también menciona composiciones y métodos para tratar la artritis reumatoidea empleando un compuesto de fórmula I o combinaciones con otro agente que tenga actividad contra la artritis.

La respuesta al problema técnico que se pretendía resolver, que era una composición que comprende un polipéptido IL-1ra y un agente no esteroide y que se emplea para el tratamiento de enfermedades inflamatorias, resulta obvia partiendo de las anterioridades citadas.

Como se observa, el objeto de las reivindicaciones 10 a 15 (folios: 478 a 486) de la presente 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	WO 98/32733	10 a 15	Nivel Inventivo
2	US 5874424	10 a 15	Nivel Inventivo
3	WO 99/17709	10 a 15	Nivel Inventivo
4	WO 99/17792	10 a 15	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 CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 27 OCT. 2005

CONCEPTO TÉCNICO Nº: 1655	EXAMINADOR TÉCNICO Código N°: 202005	EXAMINADOR JURÍDICO Código N°:
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554

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: 0-66883

EDICTO No. 2615

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió Resolución No. 1888 de 31-ENE-2006. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

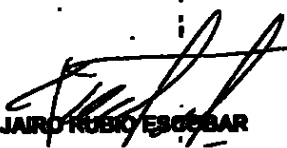
ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "TRATAMIENTO DE COMBINACION CON IL-1RA Y DIARILSULFONILUREAS QUE INHIBEN EL PROCESAMIENTO Y LA LIBERACION DE IL-1".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Carlos Olarte, o a quien haga sus veces, en su calidad de apoderado de Pfizer Products Inc., entregándole copia de la misma, advirtiéndole que contra ella proceda 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 31 ENE 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIRO 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 8:30 a.m. de hoy.

Secretaría General Ad-Hoc 16-FEB-2006 Este edicto se desfija hoy 01-MAR-2006 a las cinco (5:00 p.m.)
Secretaría General Ad-Hoc
EDICTO No. 2615