

1007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-053380-00003-0000

Fecha: 2008-04-24 17:04:12 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

AS: 101.199

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

REF.: Expediente No. 06 053380 - Solicitud de Patente FASE NACIONAL
Corresp. a la Solicitud Internacional PCT/US20005/036859
a nombre de: **BRISTOL - MYERS SQUIBB COMPANY**
Titulada: ANTAGONISTA DEL RECEPTOR DE PÉPTIDO RELACIONADO CON EL
GEN DE LA CALCITONINA

JUAN PABLO CADENA SARMIENTO, vecino de Bogotá, portador de la tarjeta profesional No. 57492 del Consejo Superior de la Judicatura, obrando como apoderado de la sociedad **BRISTOL - MYERS SQUIBB COMPANY**, según lo acredita el documento de poder presentado en esa División, de acuerdo con el Artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito solicitar que se examine si la invención contenida en la solicitud en referencia es patentable.

De acuerdo con lo anterior, me permito anexar el recibo oficial de caja No. 08-26.563 por valor de \$420.000.

De la Señora Jefe atentamente,

JUAN PABLO CADENA SARMIENTO

C.C. No. 80.410.337 de Usaquén

T.P. No. 57492 del C.S.J.

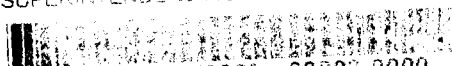
Cra 7 No. 71-21 Torre B, Piso 4

Bogotá, 23 de abril de 2008

MEV/JCN/aac

As. 101199.
1008

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 26,563
FECHA : ABRIL 2 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	2279625	02/04/2008	24,080,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		B5 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
		TOTAL :	\$ 420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-53380

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **581** DE

FECHA **31 DE OCTUBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **31 DE ENERO DE 2008**

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 X

1010

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(19) World Intellectual Property Organization
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60/393,200	1 July 2002 (01.07.2002)	US
60/413,534	25 September 2002 (25.09.2002)	US
- (71) Applicant (for all designated States except US): BRISTOL-MYERS SQUIBB COMPANY [US/US]; P. O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): CHATURVEDULA, Prasad, V. [US/US]; 190 Lancaster Way, Cheshire, CT 06410 (US). CHEN, Ling [CN/US]; 193 McCormick Lane, Middletown, CT 06457 (US). CIVIELLO, Rita [US/US]; 90 Cow Hill Road, Killingworth, CT 06419 (US). CONWAY, Charles, Mark [US/US]; 825 Farmington Drive, Cheshire, CT 06410 (US). DEGNAN, Andrew, P. [US/US]; 123 York Street, Apt. 22-P, New Haven, CT 06511 (US). DUBOWCHIK, Gene, M. [US/US]; 65 Spring Street, Middlefield, CT 06455 (US). HAN, Xiaojun [CN/US]; 65 Ridgcrest Drive, Cheshire, CT 06410 (US). KARAGEORGE,

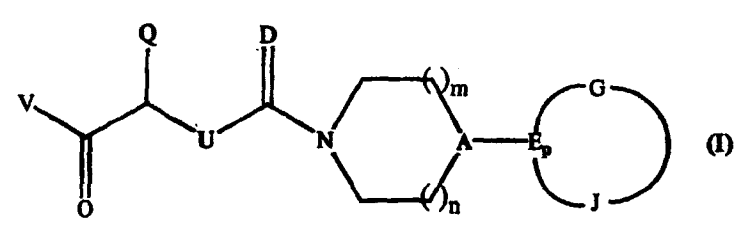
George, N. [US/US]; 34 Fox Run Road, Portland, CT 06480 (US). LUO, Guanglin [CN/US]; 135 Devonshire Lane, Madison, CT 06443 (US). MACOR, John, E. [US/US]; 644 Mosse Hill Road, Guilford, CT 06437 (US). POINDEXTER, Graham [US/US]; 15 Fox Hollow Road, Old Saybrook, CT 06475 (US). VIG, Shikha [IN/US]; 15 Park Place, Durham, CT 06422 (US).

- (74) Agents: MAKUJINA, Shah et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

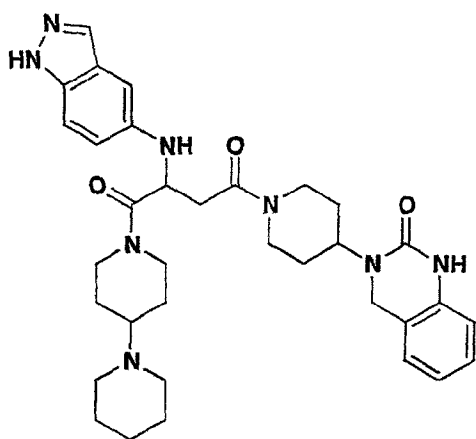
(54) Title: CALCITONIN GENE RELATED PEPTIDE RECEPTOR ANTAGONISTS



(57) Abstract: The present invention relates to compounds of Formula (I), as antagonists of calcitonin gene-related peptide receptors ("CGRP-receptor"), pharmaceutical compositions comprising them, methods for identifying them, methods of treatment using them and their use in therapy for treatment of neurogenic vasodilation, neurogenic inflammation, migraine and other headaches, thermal injury, circulatory shock, flushing associated with menopause, airway inflammatory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), and other conditions the treatment of which can be effected by the antagonism of CGRP-receptors.

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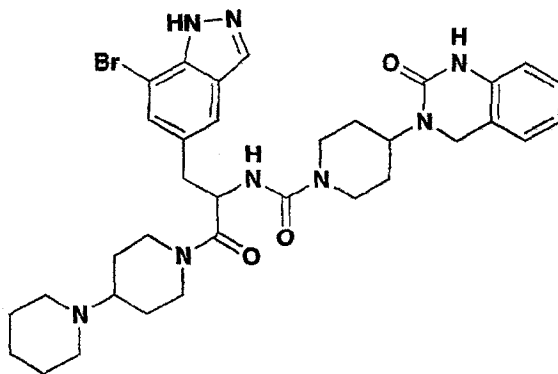
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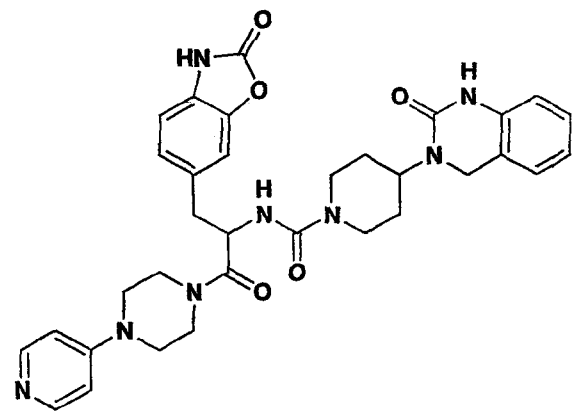
To a solution of 2-(1H-indazol-5-ylamino)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyric acid ethyl ester (0.069 mmol) in dimethylformamide (0.5 mL) in a capped drum vial was added piperidinylpiperidine
 5 (14.3 mg, 0.076 mmol, 1.1 equiv), DEPBT (22.8 mg, 1.1 equiv) and triethylamine (8 drops, ca. 160 μ L). The mixture was stirred at room temperature overnight. The final product was purified by preparative HPLC to afford the desired product (15 mg, 26% for two steps) as a tan solid. LC/MS: t_R = 0.917 min, 613.54 (MH)⁺.

10 Among other compounds envisaged within the present invention and capable of being made according to the description provided herein or those methods known to those skilled in the art include the following prophetic examples:

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-
 15 [1,4']bipiperidinyl-1'-yl-1-(7-bromo-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide

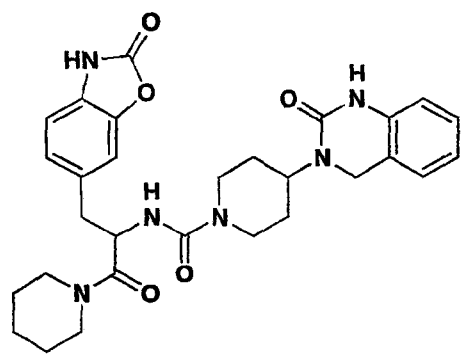


4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide

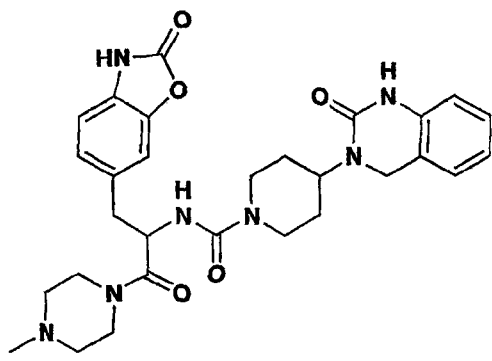


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4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-piperidin-1-yl-ethyl]-amide

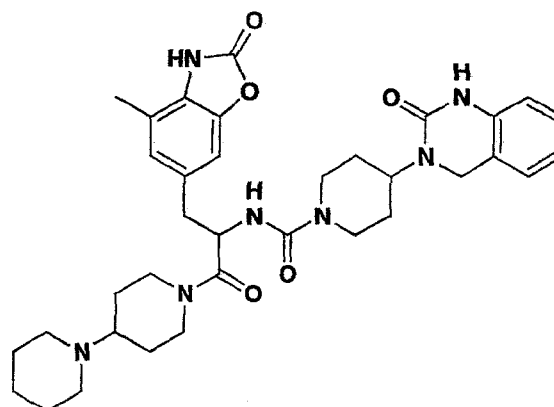


10 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-methyl-piperazin-1-yl)-2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-ethyl]-amide



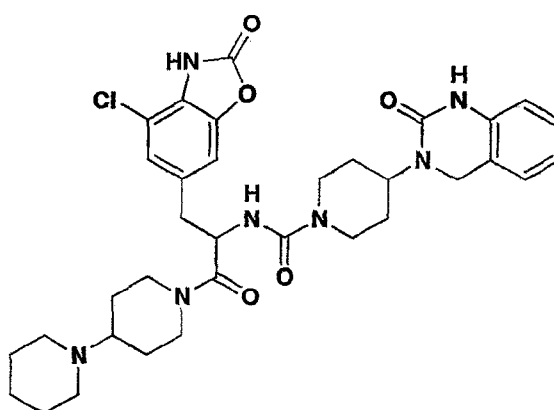
-242-

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidiny-1'-yl-1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide



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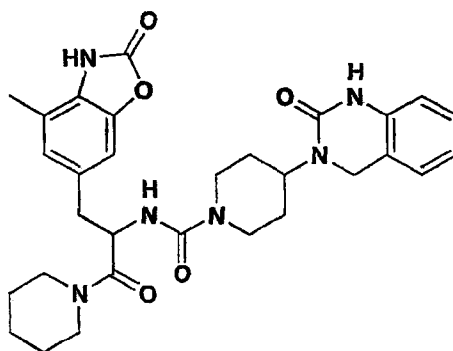
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidiny-1'-yl-1-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide



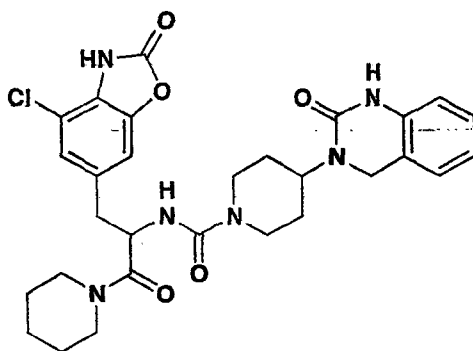
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4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-amide

-243-

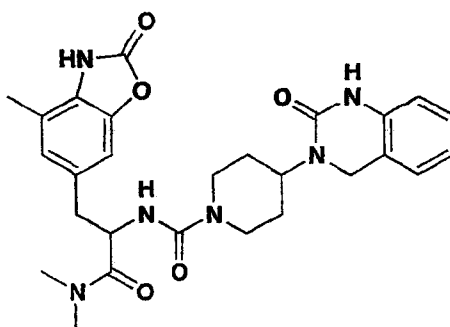


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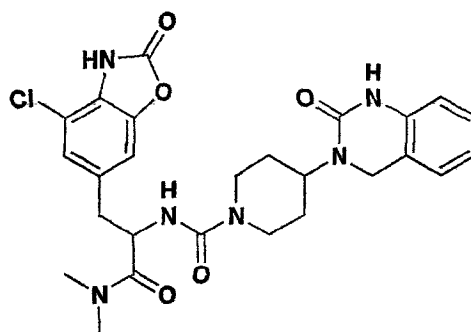
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-dimethylcarbamoyl-2-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-yl)-ethyl]-amide



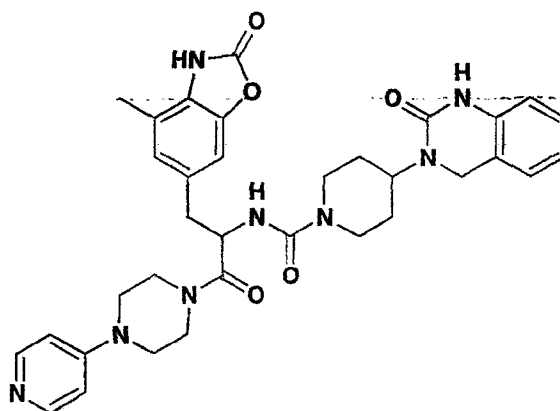
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4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl)-1-dimethylcarbamoyl-ethyl]-amide

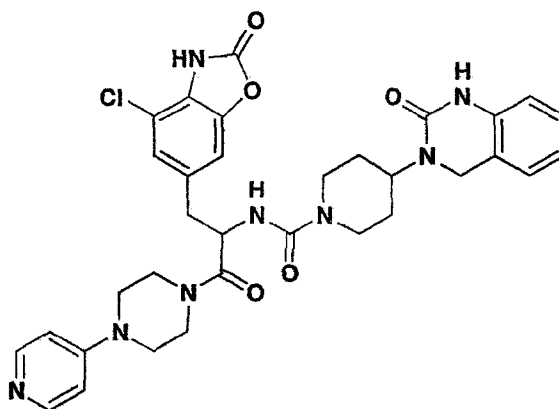
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4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide

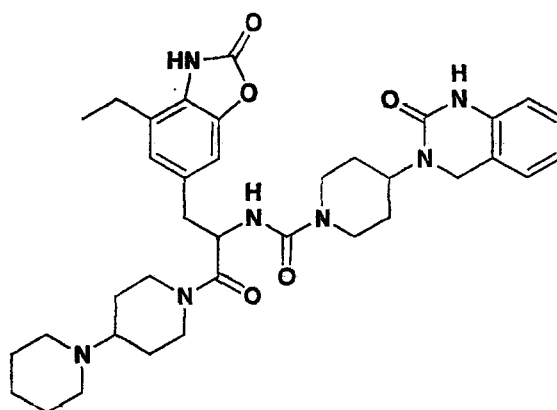


4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide



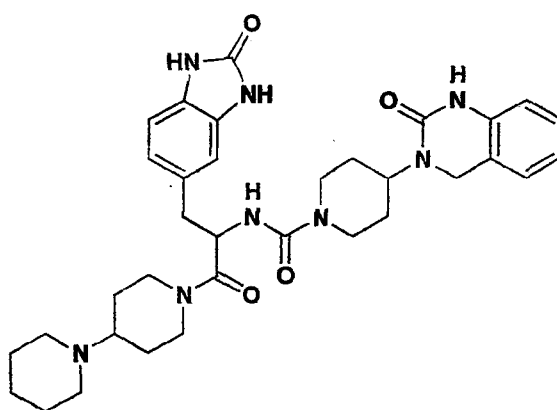
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4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidiny-1'-yl-1-(4-ethyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide



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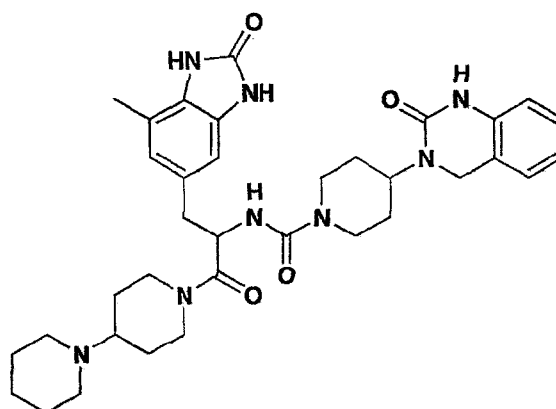
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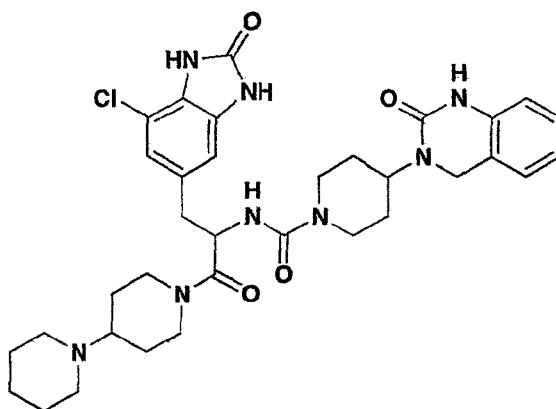
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4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidiny-1'-yl-1-(7-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide

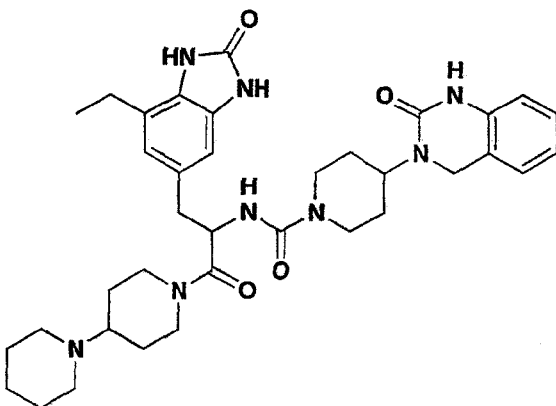
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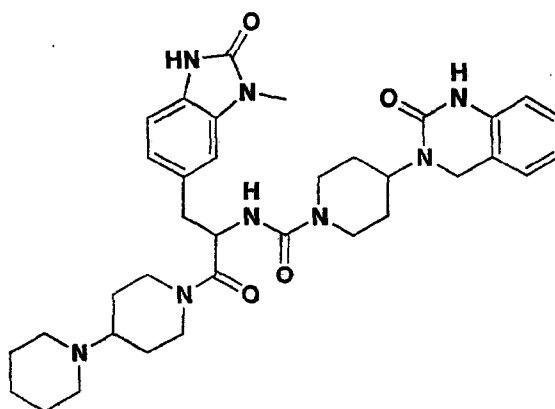
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidiny-1'-yl-1-(7-chloro-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide



4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidiny-1'-yl-1-(7-ethyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide

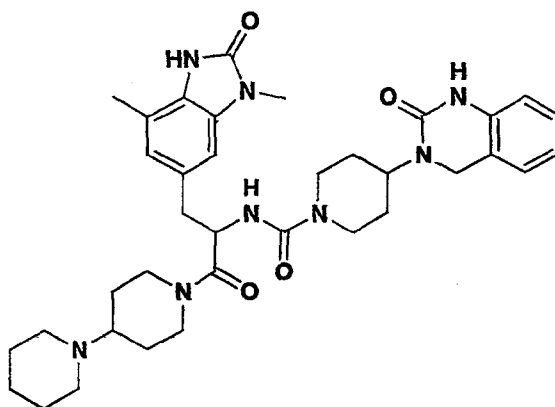


4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidiny-1'-yl-1-(3-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide



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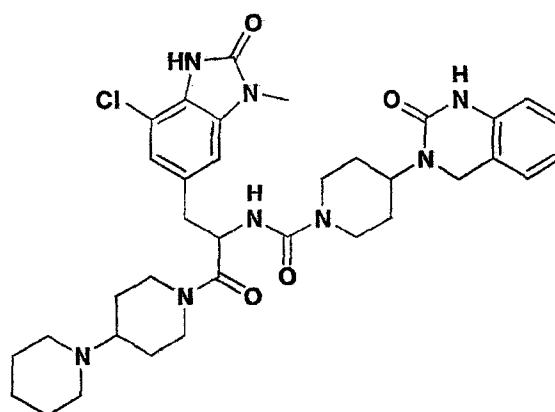
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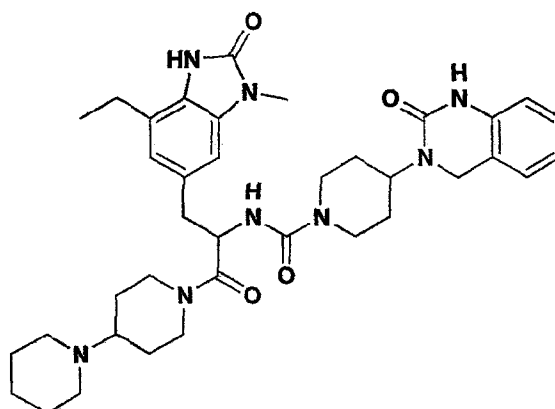
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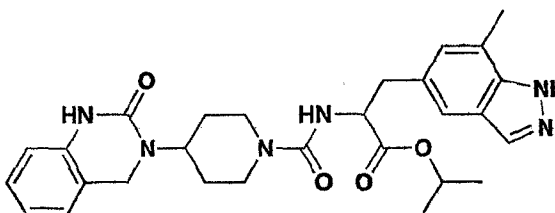
-248-



4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-
[1,4]bipiperidiny-1'-yl-1-(7-ethyl-3-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-
5 ylmethyl)-2-oxo-ethyl]-amide



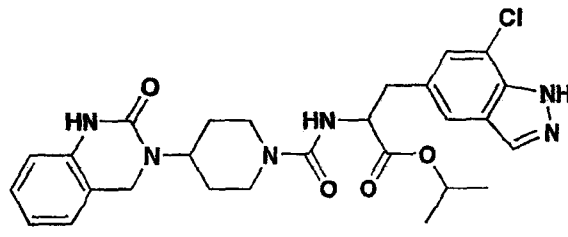
3-(7-Methyl-1H-indazol-5-yl)-2-[[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-
piperidine-1-carbonyl]-amino]-propionic acid isopropyl ester



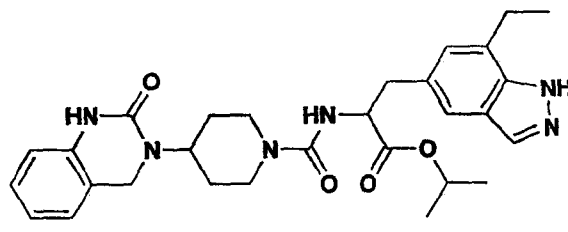
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3-(7-Chloro-1H-indazol-5-yl)-2-[[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-
piperidine-1-carbonyl]-amino]-propionic acid isopropyl ester

-249-

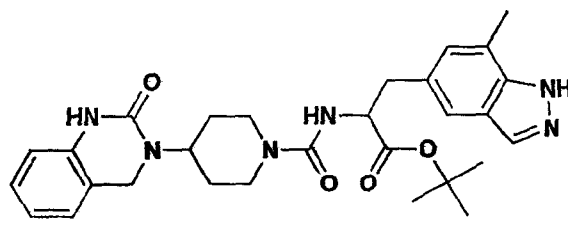


3-(7-Ethyl-1H-indazol-5-yl)-2-([4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino)-propionic acid isopropyl ester



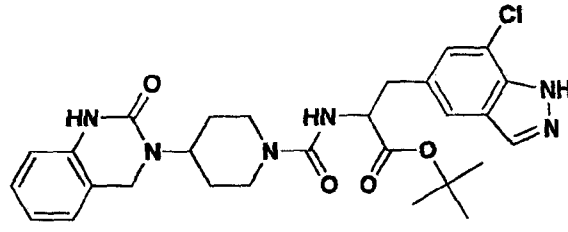
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3-(7-Methyl-1H-indazol-5-yl)-2-([4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino)-propionic acid tert-butyl ester



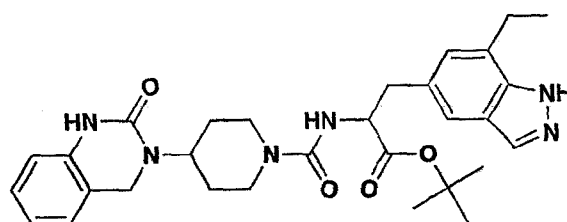
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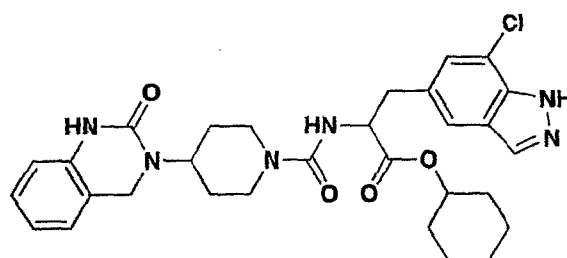


15 3-(7-Ethyl-1H-indazol-5-yl)-2-([4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino)-propionic acid tert-butyl ester

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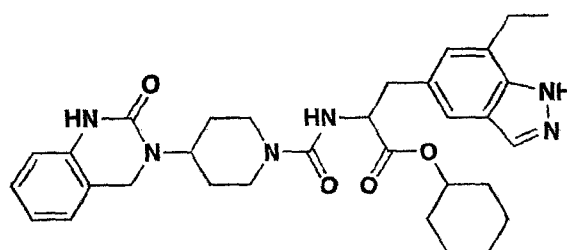


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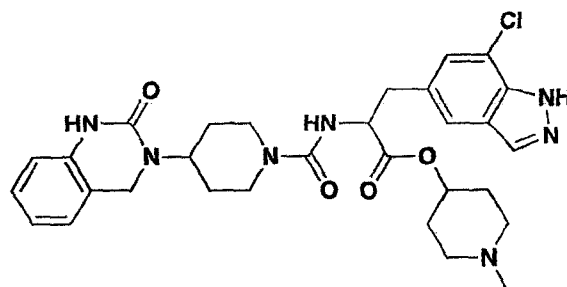
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3-(7-Ethyl-1H-indazol-5-yl)-2-([4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino)-propionic acid cyclohexyl ester



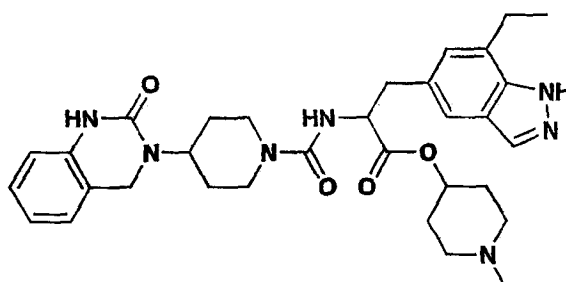
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3-(7-Chloro-1H-indazol-5-yl)-2-([4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino)-propionic acid 1-methyl-piperidin-4-yl ester

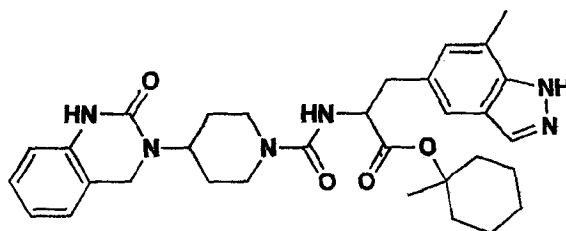


15 3-(7-Ethyl-1H-indazol-5-yl)-2-([4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino)-propionic acid 1-methyl-piperidin-4-yl ester

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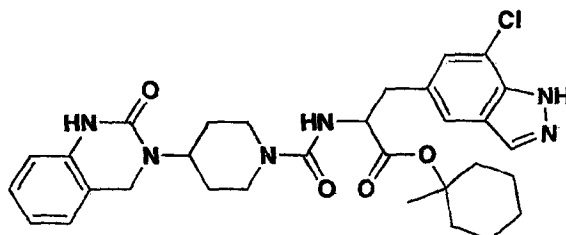


3-(7-Methyl-1H-indazol-5-yl)-2-([4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino)-propionic acid 1-methyl-cyclohexyl ester



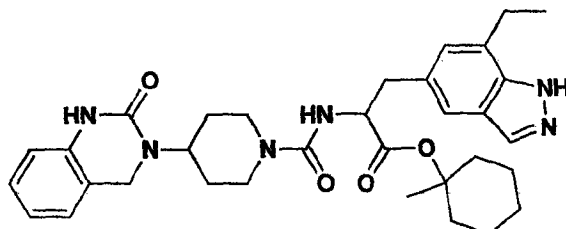
5

3-(7-Chloro-1H-indazol-5-yl)-2-([4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino)-propionic acid 1-methyl-cyclohexyl ester



10

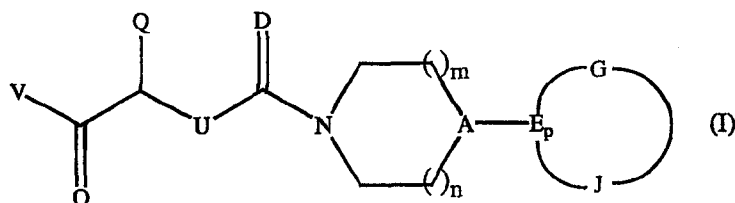
3-(7-Ethyl-1H-indazol-5-yl)-2-([4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino)-propionic acid 1-methyl-cyclohexyl ester



15 3-(7-Chloro-1H-indazol-5-yl)-2-([4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino)-propionic acid 4-phenyl-cyclohexyl ester

What is claimed is:

1. A compound according to Formula (I)



5

or a pharmaceutically acceptable salt or solvate thereof
wherein

V is -N(R¹)(R²) or OR⁴;

R⁴ is H, C₁₋₆alkyl, C₁₋₄haloalkyl or (C₁₋₄alkylene)₀₋₁R⁴

10

R⁴ is C₃₋₇cycloalkyl, phenyl, adamantyl, quinuclidyl,
azabicyclo[2.2.1]heptyl, azetidiny, tetrahydrofuranyl, furanyl,
dioxolanyl, thienyl, tetrahydrothienyl, pyrrolyl, pyrrolinyl,
pyrrolidinyl, imidazolyl, imidazoliny, imidazolidinyl,
pyrazolyl, pyrazoliny, pyrazolidinyl, oxazolyl, isoxazolyl,
thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl,
pyranyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl,
triazinyl, piperidinyl, piperazinyl, morpholino, thiomorpholino
or dioxolanyl; and

15

R⁴ is optionally substituted with 1 or 2 of the same or different
substituents selected from the group consisting of halo,
cyano, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, hydroxy,
amino, C₃₋₇cycloalkyl, C₁₋₃alkylamino, C₁₋₃dialkylamino, (C₁₋₃alkyl)₀₋₂ureido, phenyl and benzyl;
and

20

R⁴ optionally contains 1 or 2 carbonyls wherein the carbon
atom of said carbonyl is a member of the ring structure
of R⁴;

25

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R^1 and R^2 are each independently L^1 , wherein L^1 is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C_{1-6}$ alkylene-amino(C_{1-3} alkyl)₂, C_{3-7} cycloalkyl, phenyl, azetidiny, adamantyl, tetrahydrofuranyl, furanyl, dioxolanyl, thienyl, tetrahydrothienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazoliny, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyranyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, piperidinyl, piperazinyl, morpholino, thiomorpholino and dioxolanyl; and

R^1 and R^2 are each optionally and independently substituted with 1 or 2 of the same or different substituents selected from the group consisting of halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, hydroxy, amino, C_{3-7} cycloalkyl, C_{1-3} alkylamino, C_{1-3} dialkylamino, (C_{1-3} alkyl)₀₋₂ureido, phenyl and benzyl;

R^1 and R^2 optionally and independently contain 1 or 2 carbonyls wherein the carbon atom of said carbonyl is a member of the heterocycles comprising R^1 and R^2 ;

wherein L^1 is optionally and independently interrupted from the nitrogen to which it is attached by L^2 , wherein L^2 is independently C_{1-3} alkylene or C_{1-3} alkylidene; or

R^1 and R^2 together with the nitrogen to which they are attached form

X,

wherein X is azetidiny, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazoliny, imidazolidinyl, pyrazolinyl, pyrazolidinyl, azepiny, diazepiny, piperazinyl, piperidinyl, morpholino or thiomorpholino;

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provided that if X is substituted with Y, and if
X and Y are not interrupted with Z, then

X and Y optionally share one carbon
atom and together form a
spirocyclic moiety;

5

Q is Q' or Q'';

wherein

Q' is (S^y)_sR³; and

10

Q'' is NH(S^y)_sR³, NHC(O)(S^y)_sR³, NHC(O)O(S^y)_sR³ or
NHC(O)NH(S^y)_sR³;

wherein S^y is C₁₋₃alkylene or C₁₋₃alkylidene and S is 0
or 1;

U is CH₂ or NH;

15

provided that if Q is Q'', then U is CH₂;

R³ is R^{3a} or R^{3b}

wherein

R^{3a} is

20

- (i) a heterocycle having two fused rings with 5 to 7
members in each of said rings, said heterocycle
containing one to five of the same or different
heteroatoms selected from the group consisting of O, N
and S and said heterocycle optionally containing 1 or 2
carbonyls wherein the carbon atom of said carbonyl is a
member of said fused rings;

25

wherein X is optionally substituted with Y wherein Y
 is dioxolanyl, C₁₋₉alkyl, C₂₋₉alkenyl, C₂₋₉
 alkynyl, C₁₋₄alkylamino, C₁₋₄dialkylamino, C₁₋₄
 alkoxy, C₃₋₇cycloalkyl, phenyl, azetidiny, 5
 furanyl, thienyl, pyrrolyl, pyrrolinyl,
 pyrrolidinyl, pyrrolidinonyl, imidazolyl,
 imidazoliny, imidazolidinyl, imidazolidinonyl,
 pyrazolyl, pyrazoliny, pyrazolidinyl, azepiny, 10
 diazepiny, pyridyl, pyrimidinyl,
 dihydrobenzimidazolonyl, piperaziny,
 piperidinyl, morpholino, benzothiazolyl,
 benzisothiazolyl or thiomorpholino;

and wherein X and Y are
 optionally interrupted with Z, wherein Z
 is -NHC(O)O-, -NHC(O)NH⁺,
 NC(O)NH₂, -NH-, -C₁₋₃alkylene-
 , -C₁₋₃alkylene-, -C₁₋₃alkenylene-
 NHC(O)O-C₁₋₃alkylene-; and

optionally and independently substituted
 with 1 or 2 of the same or
 different substituents selected
 from the group consisting of C₁₋₄
 alkyl, amino, C₁₋₃alkylamino,
 -C₁₋₆alkylene-amino(C₁₋₃alkyl)₂,
 (C₁₋₃alkyl)₀₋₂ureido, phenyl and
 benzyl;

X and Y optionally and independently
 contain 1 or 2 carbonyls wherein
 the carbon atom of said carbonyl
 is a member of the heterocycles
 comprising X and Y;

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- (ii) a 4 to 6 membered heterocycle containing one to three of the same or different heteroatoms selected from the group consisting of O, N and S, optionally containing 1 to 2 carbonyls, wherein the carbon atom of said carbonyl is a member of said 4 to 6 membered heterocycle;
- (iii) C₃₋₇cycloalkyl;
- (iv) carbazolyl, fluorenyl, phenyl, -O-phenyl, -O-C₁₋₄alkylene-phenyl, or naphthyl; or
- (v) C₁₋₈alkyl, C₂₋₇alkenyl, -C(O)R^{3'}, CHC(O)O-R^{3'}, CH(CH₃)C(O)O-R^{3'}, -C(O)O-R^{3'} or C₂₋₇alkynyl; and

wherein R^{3a} is optionally substituted with 1 to 3 of the same or different substituents selected from the group consisting of benzyl, phenyl, -O-phenyl, -O-C₁₋₃alkylenephennyl, -C₁₋₃alkylene-OC(O)-phenyl, cyano, amino, nitro, halo, C₁₋₆alkyl, C₁₋₃mono-bi-tri-haloalkyl, C₁₋₃mono-bi-tri-haloalkyloxy, (C₁₋₃alkyl)₁₋₂amine, -OR^{3'}, -C(O)R^{3'}, -C(O)O-R^{3'}, -O-C(O)R^{3'}, -N(R^{3'})₂, -C(O)N(R^{3'})₂, -N(R^{3'})C(O)(R^{3'})₂, -N(R^{3'})C(O)N(R^{3'})₂, -N(R^{3'})C(O)OR^{3'}, -O-C(O)N(R^{3'})₂, -N(R^{3'})SO₂R^{3'}, -SO₂N(R^{3'})₂ and -SO₂R^{3'};

R^{3'} is H or -C₁₋₆alkyl;

provided that if R^{3a} is , -C(O)R^{3'}, CHC(O)O-R^{3'}, CH(CH₃)C(O)O-R^{3'} or -C(O)O-R^{3'}, then said -C(O)R^{3'}, CHC(O)O-R^{3'}, CH(CH₃)C(O)O-R^{3'} or -C(O)O-R^{3'} are unsubstituted;

R^{3b} is R^{3a} but is not phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-1-naphthyl, 1H-indol-3-yl, 1-methyl-1H-indol-3-yl, 1-formyl-1H-indol-3-yl, 1-(1,1-

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dimethylethoxycarbonyl)-1H-indol-3-yl, 4-imidazolyl,
1-methyl-4-imidazolyl, 2-thienyl, 3-thienyl, thiazolyl,
1H-indazol-3-yl, 1-methyl-1H-indazol-3-yl,
benzo[b]fur-3-yl, benzo[b]thien-3-yl, pyridinyl,
quinolinyl or isoquinolinyl; optionally substituted in
the carbon skeleton with mono-, di- or trisubstituted by
fluorine, chlorine or bromine atoms or by branched or
unbranched alkyl groups, C₃₋₈-cycloalkyl groups,
phenylalkyl groups, alkenyl, alkoxy, phenyl,
phenylalkoxy, trifluoromethyl, alkoxycarbonylalkyl,
carboxyalkyl, alkoxycarbonyl, carboxy,
dialkylaminoalkyl, dialkylaminoalkoxy, hydroxy, nitro,
amino, acetyl amino; propionyl amino, benzoyl,
benzoylamino, benzoylmethylamino,
methylsulphonyloxy, aminocarbonyl,
alkylaminocarbonyl, dialkylaminocarbonyl, alkanoyl,
cyano, tetrazolyl, phenyl, pyridinyl, thiazolyl, furyl,
trifluoromethoxy, trifluoromethylthio,
trifluoromethylsulphinyl- or trifluoromethylsulphonyl
groups;

wherein said substituents may be the same or different
and the above-mentioned benzoyl,
benzoylamino- and benzoylmethylamino groups
may in turn additionally be substituted in the
phenyl moiety by a fluorine, chlorine or
bromine atom, or by an alkyl, trifluoromethyl,
amino or acetyl amino group;

D is O, NCN or NSO₂C₁₋₃alkyl;

A is C, N or CH;

m and n are independently 0, 1 or 2;

provided that

if m and n are 0, then A is not N;

if m is 2, then n is not 2; or

if n is 2, then m is not 2;

E is N, CH or C;

5

p is 0 or 1;

if p is 1, then G, J and E together form A^x or A^y.

10

A^x is a fused heterocycle having two fused rings with 5 to 7 members in each of said rings, said heterocycle containing one to four of the same or different heteroatoms selected from the group consisting of O, N and S; and

optionally containing 1 or 2 carbonyls wherein the carbon atom of said carbonyl is a member of said fused heterocycle;

15

A^y is a 4 to 6 membered heterocycle containing one to three heteroatoms selected from the group consisting of O, N and S; and

optionally containing 1 to 2 carbonyls, wherein the carbon atom of said carbonyl is a member of said 4 to 6 membered heterocycle;

20

wherein A^x and A^y are optionally substituted with C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄haloalkyl, cyano, C₃₋₇cycloalkyl, phenyl, halophenyl, halo, furanyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, pyridyl, pyrimidinyl, piperidinyl, piperazinyl or morpholino; or

25

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if p is 0 such that G and J are each attached to A, then A is C, and G, J and A together form a spirocyclic ring system with said rings of said system containing A and wherein G, J and A together are GJA' or GJA";

5 wherein

GJA' is A^x or A^y; and

GJA" is A^x or A^y;

provided that

A^x is not a 1,3-diaza-fused heterocycle;

10 and

A^y is not a 1,3-diaza-heterocycle;

and further provided that

if Q is Q", then R³ is R^{3a}; and

if Q is Q', then

15 R³ is R^{3b}; or

R³ is R^{3a}, p is 0 and G, J and A together form GJA".

2. A compound according to claim 1, wherein Q is Q' and R³ is R^{3b}.
3. A compound according to claim 1, wherein Q is Q', R³ is R^{3a} and p is 0 such that G, J and A together form GJA".
- 20 4. A compound according to claims 2 or 3, wherein Q is Q' and U is CH₂.
5. A compound according to claims 2 or 3, wherein Q is Q' and U is NH.
6. A compound according to claim 1, wherein Q is Q".
7. A compound according to claim 6, wherein Q" is NH(S^y)_sR³.
8. A compound according to claim 6, wherein Q" is NHC(O)(S^y)_sR³.
- 25 9. A compound according to claim 6, wherein Q" is NHC(O)O(S^y)_sR³.
10. A compound according to claim 6, wherein Q" is NHC(O)NH(S^y)_sR³.
11. A compound according to claim 1, wherein V is OR⁴.

12. A compound according to claim 1, wherein V is $-N(R^1)(R^2)$.
13. A compound according to claim 1, wherein R^4 is H, C_{1-6} alkyl or $(C_{1-4}$ alkylene)₀, R^4 and R^4 is C_{3-7} cycloalkyl.

14. A compound according to claim 1, wherein V is $-N(R^1)(R^2)$ and

5 R^1 and R^2 are each independently L^1 , wherein L^1 is selected from the group consisting of H, C_{1-6} alkyl, $-C_{1-6}$ alkylene-amino(C_{1-3} alkyl)₂, C_{3-7} cycloalkyl, phenyl, azetidiny, adamantyl, tetrahydrofuranyl, furanyl, dioxolanyl, thienyl, tetrahydrothienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazoliny, imidazolidiny, pyrazolyl, 10 pyrazolinyl, pyrazolidiny, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyranyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, piperidinyl, piperazinyl, morpholino, thiomorpholino and dioxolanyl; or

R^1 and R^2 together with the nitrogen to which they are attached form X,

wherein X is azetidiny, pyrrolinyl, pyrrolidinyl, imidazoliny, imidazolidiny, pyrazolinyl, pyrazolidiny, azepiny, diazepiny, piperazinyl, piperidinyl, morpholino or thiomorpholino;

wherein X is substituted with Y, wherein Y is dioxolanyl, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, phenyl, azetidiny, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrrolidinonyl, imidazolyl, imidazoliny, imidazolidiny, imidazolidinonyl, pyrazolyl, pyrazolinyl, pyrazolidiny, azepiny, diazepiny, pyridyl, pyrimidinyl, dihydrobenzimidazolonyl, piperazinyl, piperidinyl, morpholino,

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benzothiazolyl, benzisothiazolyl or
thiomorpholino;

and wherein X and Y optionally share one
carbon atom and together form a
spirocyclic moiety.

5

14. A compound according to claim 1, wherein wherein V is $-N(R^1)(R^2)$ and
 R^1 and R^2 are each independently L^1 , wherein L^1 is selected from the
group consisting of H, C_{1-6} alkyl, or

R^1 and R^2 together with the nitrogen to which they are attached form
X,

10

wherein X is piperidinyl or morpholino;

wherein X is substituted with Y, wherein Y is
dioxolanyl, C_{1-4} alkyl or piperidinyl;

and wherein X and Y optionally share one
carbon atom and together form a
spirocyclic moiety.

15

15. A compound according to claim 1, wherein V is $-N(R^1)(R^2)$ and wherein R^1 and
 R^2 are each independently L^1 , wherein L^1 is selected from the group consisting of
H, C_{1-6} alkyl.

20 16. A compound according to claim 1, wherein V is $-N(R^1)(R^2)$ and wherein
 R^1 and R^2 together with the nitrogen to which they are attached form
X,

wherein X is piperidinyl or morpholino;

wherein X is substituted with Y, wherein Y is
dioxolanyl, C_{1-4} alkyl or piperidinyl;

25

and wherein X and Y optionally share one
carbon atom and together form a
spirocyclic moiety.

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16. A compound according to claim 1, wherein V is $-N(R^1)(R^2)$ and wherein
R¹ and R² together with the nitrogen to which they are attached form
X,
wherein X is piperidinyl;
5 wherein X is substituted with Y, wherein Y is
piperidinyl.
17. A compound according to claim 1, wherein V is $-N(R^1)(R^2)$ and wherein
R¹ and R² together with the nitrogen to which they are attached form
X,
10 wherein X is morpholino;
wherein X is substituted with Y, wherein Y is C₁₋₄alkyl.
18. A compound according to claim 1, wherein V is $-N(R^1)(R^2)$ and wherein
R¹ and R² together with the nitrogen to which they are attached form
X,
15 wherein X is piperidinyl;
wherein X is substituted with Y, wherein Y is C₁₋₄alkyl.
19. A compound according to claim 1, wherein V is $-N(R^1)(R^2)$ and wherein
R¹ and R² together with the nitrogen to which they are attached form
X,
20 wherein X is piperidinyl;
wherein X is substituted with Y, wherein Y is
dioxolanyl;
and wherein X and Y share one carbon atom and
together form a spirocyclic moiety.
- 25 20. A compound according to claim 1, wherein R³ is R^{3a} and R^{3a} is substituted or
unsubstituted phenyl, hydroxyphenyl, azetidiny, naphthyl, C₁₋₆alkyl, C₂₋₆alkenyl,
C₂₋₆alkynyl, dihydroquinolinonyl, hydroquinolinonyl, quinolinyl,

- dihydroisoquinolinonyl, hydroisoquinolinonyl, isoquinolinyl,
 dihydroquinazolinonyl, hydroquinazolinonyl, quinazolinyl,
 dihydroquinoxalinonyl, hydroquinoxalinonyl, quinoxalinyl, benzimidazolyl,
 indazolyl, dihydrobenzimidazolonyl, hydrobenzimidazolonyl, benzimidazoliny,
- 5 dihydro-benzthiazolonyl, hydrobenzthiazolonyl, benzthiazolyl,
 dihydrobenzoxazolyl, benzotriazolyl, dihydrobenzothiophenonyl,
 hydrobenzothiophenonyl, benzothienyl, dihydrobenzofuranonyl,
 hydrobenzofuranonyl, benzofuranyl, benzdioxolanyl, dihydroindolonyl,
 hydroindolonyl, indolyl, indoliziny, isoindolyl, indoliny, indazolyl, pyrazolyl,
- 10 pyrazolinyl, pyrazolidiny, furanyl, thienyl, pyrrolyl, pyrroliny, pyrrolidinyl,
 imidazolyl, imidazoliny, imidazolidiny, pyridyl, puriny, carbazolyl,
 pyrimidinyl, piperidinyl, triazolopyrimidinyl, tetrahydropyrazolopyridiny,
 piperazinyl or morpholino.
21. A compound according to claim 1, wherein R^3 is R^{3b} and R^{3b} is substituted or
- 15 unsubstituted dihydrobenzimidazolonyl, hydrobenzimidazolonyl,
 benzimidazoliny, dihydro-benzthiazolonyl, hydrobenzthiazolonyl,
 benzthiazolyl, dihydrobenzothiophenonyl, hydrobenzothiophenonyl,
 dihydrobenzofuranonyl, hydrobenzofuranonyl, 1H-indazol-5-yl, benzdioxolanyl,
 dihydrobenzoxazolyl, benzotriazolyl, dihydroindolonyl, hydroindolonyl,
- 20 indoliziny, isoindolyl, indoliny, pyrazolyl, pyrazolinyl, pyrazolidiny, furanyl,
 pyrrolyl, pyrroliny, pyrrolidinyl, imidazoliny, imidazolidiny, puriny,
 carbazolyl, pyrimidinyl, piperidinyl, piperazinyl or morpholino; optionally
 substituted as provided in the first embodiment of the first aspect.
22. A compound according to claim 1, wherein D is O and m and n are each 1.
- 25 23. A compound according to claim 1, wherein p is 1; and G, J and E together form
 A^x or A^y .
24. A compound according to claim 1, wherein p is 0 such that G and J are each
 attached to A, then A is C and G, J and A together form a spirocyclic ring system
 with said rings of said system containing A and wherein G, J and A together are
- 30 GJA' or GJA".
25. A compound according to claim 1, wherein p is 0 such that G and J are each
 attached to A, then A is C and G, J and A together form a spirocyclic ring system

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3a} and R^{3a} is phenyl, naphthyl, indazolyl, benzimidazolyl, dihydrobenzoxazolyl, benzotriazolyl, benzothienyl, benzdioxolanyl, dihydroindolonyl, indolyl, furanyl, thienyl, pyridyl, purinyl, carbazolyl, piperidinyl, triazolopyrimidinyl, tetrahydropyrazolopyridinyl; optionally substituted as provided in the first embodiment of the first aspect.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3a} and R^{3a} is dihydro-benzthiazolonyl, hydrobenzthiazolonyl, benzthiazolyl, dihydrobenzothiophenonyl, hydrobenzothiophenonyl, benzothienyl, dihydrobenzofuranonyl, hydrobenzofuranonyl, benzofuranyl, dihydroindolonyl, hydroindolonyl, indolyl, indoliziny, isoindolyl, indolinyl or indazolyl; optionally substituted as provided in the first embodiment of the first aspect.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3a} and R^{3a} is dihydrobenzoxazolyl, benzotriazolyl, indolyl, halonitrophenyl, halopyrimidine, halopurinyl, C_{1-3} alkyl-nitroaminopyrimidine, triazolopyrimidinyl, pyridyl, indazolyl, phenyl or benzdioxolanyl; optionally substituted as provided in the first embodiment of the first aspect.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3a} and R^{3a} is naphthyl, phenyl-O-phenyl, or thienyl; optionally substituted as provided in the first embodiment of the first aspect.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3b} .

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3b} and R^{3b} is

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

2020
Bogotá, D.C.,

Abogado

JUAN PABLO CADENA SARMIENTO.

ASUNTO	Radicación	06053380
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	<u>0</u> <u>4</u> <u>8</u> <u>4</u> <u>1</u>
	Folios	<u>018</u>

Patente de Invención



Patente de Modelo de Utilidad



Vía Nacional



Vía PCT (fase nacional)



Cap. I



Cap. II



No. Sol. Internacional

PCT/US2003/038799

Fecha de Presentación Internal.

05-12-2003

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

Descripción: Folios: 362 a 872 (como se radicó inicialmente)

Reivindicaciones: Folios: 873 a 917 (como se radicó inicialmente)

Dibujos: Folios: 919 a 922 como se radicó inicialmente

Objeto de la invención

Título de la solicitud: Antagonistas del receptor de peptido relacionado con el gen de calcitonina.

El objeto de la presente solicitud de patente de invención consiste en:

Compuestos antagonistas del receptor de péptido relacionado con el gen de calcitonina.

Expediente 2006 053380. primer 45

- Reivindicación 1 : Un compuesto seleccionado de acuerdo a lo divulgado en los folios 873 a 883.
- Reivindicación 2 : Un compuesto seleccionado de acuerdo a lo divulgado en los folios 883 a 887.
- Reivindicación 3 : Una composición que comprende una serie de compuestos según lo divulgado en los folios 887 a 897.
- Reivindicación 4: Una composición que comprende una serie de compuestos según lo divulgado en los folios 898 a 902 .

Reivindicaciones 5 y 6 : De uso.

El problema planteado en esta solicitud es la necesidad proporcionar compuestos antagonistas del receptor de peptido relacionado con el gen de calcitonina, útiles en el tratamiento de vasolidatación neurogénica, migraña, dolor de cabeza en racimo, entre otras.

Para solucionar este problema técnico la solicitud en estudio proporciona los compuestos divulgados en las reivindicaciones 1 y 2.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la Clasificación Internacional de Patentes (IPC): A61P25/06; A61K31/535; A61K31/52; C07D239/00; C07D243/10.

Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)

Se aclara que, de acuerdo con el Art 14, el uso de las reivindicaciones 5 y 6 , no es patentable .

Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente la cual presenta fecha de publicación del 21-07-2005, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud :

Nº	Documento	Título	Fecha de publicación
D1	WO03/104236	CALCITONIN GENE RELATED PEPTIDE RECEPTOR ANTAGONISTS.	1-4

Análisis de patentabilidad (artículo 14 D486)

Novedad (artículo 16 D486)

Respecto a la solicitud en estudio

La reivindicación 1 dice : "Un compuesto seleccionado de acuerdo a lo divulgado en los folios 873 a 883".

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La reivindicación 2 dice : "Un compuesto seleccionado de acuerdo a lo divulgado en los folios 883 a 887".

La reivindicación 3 dice : "Una composición que comprende una serie de compuestos según lo divulgado en los folios 887 a 897".

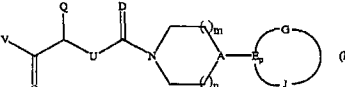
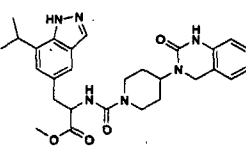
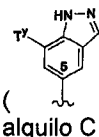
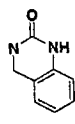
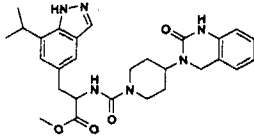
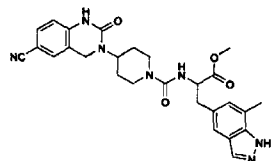
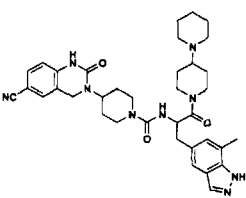
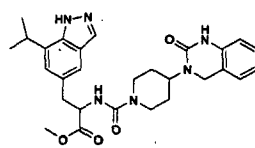
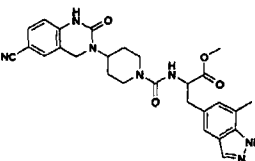
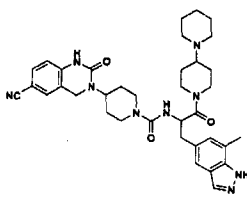
La reivindicación 4 dice : "Una composición que comprende una serie de compuestos según lo divulgado en los folios 898 a 902".

Respecto a la solicitud en estudio

- Al comparar elemento por elemento el objeto de la presente solicitud con el estado de la técnica, esta oficina encuentra:

D1 divulga compuestos antagonistas del receptor de peptido relacionado con el gen de calcitonina, útiles en el tratamiento de vasolidatación neurogénica, migraña, dolor de cabeza en racimo, entre otras.

Para las reivindicaciones 1 y 3 .

SOLICITUD	D1.
Según la reivindicación 1	 Según la reivindicación 1. V es -N(R¹)(R²) y R¹ y R² forman X y X es piperidinil , en donde X esta sustituido por Y y Y es piperidinil o V es OR⁴ y R⁴ es alquilo C₁₋₆  Q es Q' y Q' es (S')_sR³ donde : S' es alquilenos C₁₋₃ y s es 1 R³ es R^{3b} es R^{3a} : un heterociclo que tiene 2 anillos fusionados con de 5 hasta 7 miembros en cada uno de los anillos, con uno a cinco de los mismos o diferentes heteroátomos seleccionados de O,N o S.  () . 1H-indazol-5-il, T^y es alquilo C₁₋₄ U es NH A es CH. m y n son 1. E es N. p es 1. G, J y E forman Ax un heterociclo que tiene 2 anillos fusionados con de 5 hasta 7 miembros en cada uno de los anillos, con uno a cinco de los mismos o diferentes heteroátomos seleccionados de O,N o S.y opcionalmente contiene 1 o 2 carbonilos en donde el átomo de carbono del carbonilo es un miembro del heterociclo fusionado  ,opcionalmente sustituido por ciano
 Ester de metilo del ácido (+)-3-(7-isopropil-1H-indazol-5-il)-2-[[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino]-propiónico. Ejemplo 205.  Ester de metilo del ácido (+)-2-[4-(6-ciano-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino]-3-(7-metil-1H-indazol-5-il) propiónico. . Ejemplo 210.  {2-[1,4']bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il-metil)-2-oxo-etil)-amida del ácido (+)-4-(6-ciano-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico . Ejemplo 211.	  

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Que D1 (reivindicación 1 ,Folio 1017, página 276, línea 8 , definición para V, línea 9, definición de R⁴; Folio 1017A, página 277, líneas 24-26,29, definición de R¹ y R² ; Folio 1018, página 279, líneas 6 a 8, 11-12,16, Folio 1018A , página 278, líneas 1,10, Folio 1023A, página 28, definición de Q; Folio 1020, página 282, líneas 4-14y 21-22, definición de E,p,G,J y E) ya encierra compuestos reclamados bajo las reivindicaciones 1 y 3 , tal como se expone en el cuadro comparativo.

Para las reivindicaciones 2 y 4

D1 enseña con ejemplos específicos los compuestos listados en la reivindicación 2 y la reivindicación 4 de la presente solicitud (página 240 línea 14 a página 252, línea 5, Ver folios 1010A -1016A)

En consecuencia los compuestos reclamados y las composiciones farmacéuticas que los contienen de las reivindicaciones 1 a 4 , se encuentran ya cubiertos por el alcance de D1 y no son nuevos.

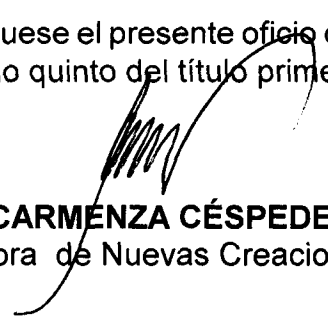
Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	WO03/104236	1-4	Novedad

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 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

Directora de Nuevas Creaciones (C).

El anterior requerimiento fue notificado por fijación en lista, de fecha
09 ABR, 2010

CONCEPTO TÉCNICO No. 438	EXAMINADOR TÉCNICO Código No. 202075
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