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Señora

Alix Carmenza Céspedes de Vergel

Jefe de División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-101178- -00002-0000

Dep. 2020 NUECRLACION: 378 FASLNACIONALI
notos: 2

Referencia: Expediente No. 06.101.178

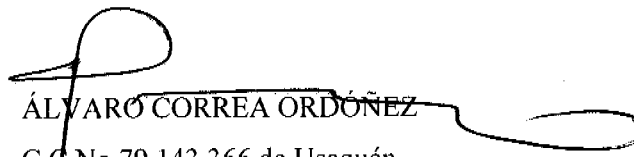
Solicitud de Patente de Invención titulada: "Formulaciones de dispersiones sólidas de acetato de bazedoxifeno"

Solicitante: Wyeth

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN EL ARTÍCULO 44 DE LA DECISIÓN
486. GACETA NO. 577

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado de la sociedad arriba mencionada, solicito que se examine la invención de la referencia según los requisitos de patentabilidad previstos en la Decisión 486 de la Comisión de la Comunidad Andina de Naciones. Adjunto recibo de caja por valor de \$404.000 para cubrir la tasa correspondiente según la Resolución 36155 del 28 de diciembre de 2006.

Atentamente,


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

Anexo: Recibo de caja por valor de \$404.000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176087-2

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RECIBO OFICIAL DE CAJA : 07 - 90,100
FECHA : NOVIEMBRE 1 DE 2007

SUPLENTE



Excmo.
H. E.
A. E.

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
RAISBECK LARA RODRIGUEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	55868294	01/11/2007	34,131,400.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN
			404,000.00
		TOTAL :	\$ 404,000.00

SON: CUATROCIENTOS CUATRO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-101178

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **577** DE

FECHA **29 DE JUNIO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

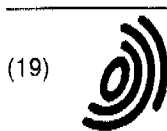
EXPIRA EL **27 DE SEPTIEMBRE DE 2007**

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



(19)

Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 1 336 602 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
20.08.2003 Bulletin 2003/34

(51) Int Cl.7: **C07C 205/00, A61K 31/00**(21) Application number: **02425075.5**(22) Date of filing: **13.02.2002**

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR**
Designated Extension States:
AL LT LV MK RO SI

(71) Applicant: **Scaramuzzino, Giovanni**
20052 Monza (Milano) (IT)

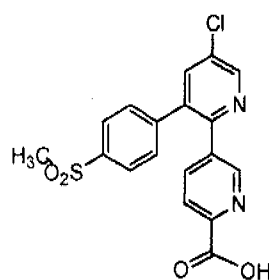
(72) Inventor: **Scaramuzzino, Giovanni**
20052 Monza (Milano) (IT)

(54) **Nitrate prodrugs able to release nitric oxide in a controlled and selective way and their use for prevention and treatment of inflammatory, ischemic and proliferative diseases**

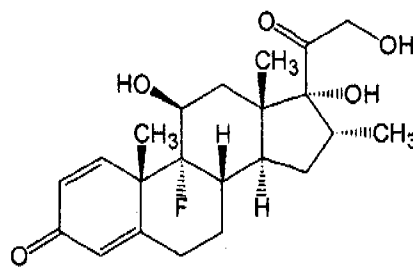
(57) New pharmaceutical compounds of general formula (I): $F-(X)_q$ where q is an integer from 1 to 5, preferably 1; -F is chosen among drugs described in the text, -X is chosen among 4 groups -M, -T, -V and -Y as described in the text.

The compounds of general formula (I) are nitrate prodrugs which can release nitric oxide in vivo in a controlled and selective way and without hypotensive side

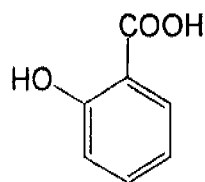
effects and for this reason they are useful for the preparation of medicines for prevention and treatment of inflammatory, ischemic, degenerative and proliferative diseases of musculoskeletal, tegumental, respiratory, gastrointestinal, genito-urinary and central nervous systems.

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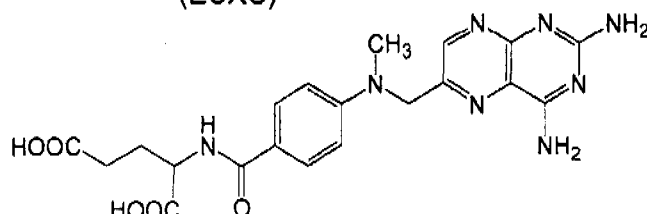
(ECLXXXVI)



(ECXC)



(ECXCI)



(ECC)

GROUP 2B:

[0046] alendronic acid, AGN-4310, arzoxifene (SXXX), avicatonin, bazedoxifene/TSE-424, bervastatin, butedronic acid, calcipotriol, calcitriol (SVIII), CGP-77675, clodronic acid, CP-336156 (SXXXII), CP-424391, doxercalciferol, droloxifene (SVI), EB-1089 (SXXXV), ecalcitriol, ED-71, EMD-84444, ERA-923, esonarimod, estradiol, etidronic acid (SXV), F-9775A, F-9775B, falecalcitriol (SXXXI), FC-1271, GW-544, HMR-3339A, 4-hydroxytamoxifene, ibandronic acid (SXX), idoxifene, incadronic acid, LGD-2226, lasofoxifene (SVII), levormeloxifene, levosimendan, lexacalcitol, lidadronic acid (SV), maxacalcitol (SXL), medronic acid, minodronic acid (SIII), miproxifene, NDE-1003, neridronic acid, NPS-2143 (SXII), NVP-AAK980, olpadronic acid (SXXI), ORG-30659, one-alpha-D₂ (SXL), ormeloxifene, osaterone, oxidronic acid, pamidronic acid (SXXII), paricalcitol (SXXXVII), pipendoxifene (SXXXIII), piridronic acid, pitavastatin, plicamycin, pralnacasan, raloxifene (SXIII), ranelic acid, risedronic acid (SXVI), RWJ-68354, SB-242784 (SIX), SB-265123, SB-267268, SB-273005, SC-56631, secalciferol, semparatide, simendan, SUN-E3001, TAK-778, teriparatide, tiludronic acid, tibolone, toremifene (SXIV), TJN-135, trimegestone, trioxifene, TSE-424, vitamina D₂ (SII), vitamina D₃, VX-745 (SX), zindoxifene, zoledronic acid (SIV), (SXI), (SXLII), (SL)

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(e.g. ulcers, aphtha, psoriasis, dermatitis, skin tumors) of respiratory system (e.g. asthma, chronic obstructive pulmonary disease, allergy, emphysema, bronchitis, ARDS, rhinitis, cystic fibrosis, lung tumors), of gastrointestinal system (e.g. peptic ulcer, duodenal ulcer, ulcerative colitis, Crohn disease, hepatic cirrhosis, pancreatitis, esophagitis, gastritis, colon familial polyposis, colon-rectum tumors, liver tumors, oesophagus tumors, pancreas tumors, stomach tumors), of genital system (e.g. benign prostatic hypertrophy, prostatitis, sexual disorders, prostate tumors, breast tumors, uterus tumors, ovary tumors), of urinary system (urinary incontinence, bladder tumors) and of central nervous system (e.g. multiple sclerosis, Alzheimer disease, brain tumours).

[0063] Compounds of general formula (I) are preferably in a completely or partially amorphized form in order to improve their bioavailability that is to increase their AUC and/or their maximum plasmatic concentration (C_{max}) or to reduce the time necessary to obtain this concentration (T_{max}). This because it is known that an amorphized compound has usually a better solubility and a better solubilization rate than the same compound in a crystallized state.

[0064] The amorphized compounds of general formula (I) are obtainable by treating these compounds with one or more excipients capable to amorphize these compounds. The techniques used for the amorphization are for example lyophilization, kneading and preferably spray-drying and co-grinding. In particular in the spray-drying technique the active principle is dissolved in a solvent, for example an alcohol, and the so obtained solution is mixed at room temperature with a solution or a suspension of excipients capable to amorphize the compounds of general formula (I). The resulting solution or suspension is treated in a spray-drying equipment. This last technique is also called solid dispersion technique and is particularly preferred.

[0065] The excipients are chosen from one of the following classes: polyalcohols (e.g. mannitol, sorbitol); monosaccharides or disaccharides (e.g. glucose, fructose, lactose), polysaccharides and their derivatives (e.g. microcrystalline cellulose, hydroxypropylmethylcellulose (HPMC)); polyvinylpyrrolidone (PVP); cyclodextrins and their derivatives (e.g. α -cyclodextrin, β -cyclodextrin, methyl- β -cyclodextrin, carboxymethyl- β -cyclodextrin, acetyl- β -cyclodextrin, 2-hydroxypropyl- γ -cyclodextrin, γ -cyclodextrin, dimethyl- β -cyclodextrin, 2-hydroxyethyl- β -cyclodextrin, 2-hydroxypropyl- β -cyclodextrin, 3-hydroxypropyl- β -cyclodextrin, trimethyl- β -cyclodextrin); agents which can increase the membrane permeability (e.g. SNAC, sodium caprinate).

[0066] Preferably they are chosen among: polyvinylpyrrolidone, hydroxypropylmethylcellulose, lactose, microcrystalline cellulose, 2-hydroxypropyl- β -cyclodextrin, 3-hydroxypropyl- β -cyclodextrin.

[0067] The necessary amorphization degree, which can be measured by a calorimetric experiment with DSC, is at least of 5 %, but preferably greater than 80%.

[0068] Thanks to this amorphization is possible to administer compounds of general formula (I), usually more lipophilic than original drugs and consequently with solubility problems, also per os (e.g. tablets, capsules) and also through a modified release formulation: in fact both conditions require a not too low solubility.

[0069] Preferably the modified release pharmaceutical formulations are parenteral, per os (diffusion systems, dissolution systems, erodable systems, osmotic systems and systems with ionic exchange resins), and transdermic release therapeutic systems (with reservoir, with membrane and with diffusion through polymeric membrane).

[0070] The compounds so obtained by spray-drying have a better bioavailability as shown by dissolution test and they can so be administered per os.

[0071] The w/w ratio among compounds of general formula (I) and the above cited excipients is preferably between 1:0,7 and 1:10.

[0072] Particularly preferred, as formulations for the compounds of this invention, are solid dispersion prepared with spray-drying technique using polyvinylpyrrolidone as excipient according to a drug/PVP ratio of 28/72 w/w.

[0073] The compounds of this invention may be administered orally, rectally, parenterally or by locally application (dermal, topical, transdermal, ocular, inhalation etc.)

[0074] The following examples are given to illustrate the invention and they are not limitative of the same.

EXAMPLE 2

Endogenous S-nitrosohemoglobin (SNO-Hb) levels in rat blood and after administration of N-[4-(5-p-tolyl-3-trifluoromethyl-1H-pyrazol-1-yl)phenylsulfonyl]-p-nitroxymethylbenzamide (Ela)

[0179] A highly sensitive photolysis-chemiluminescence methodology was used. Nitric oxide, released from Hb-SNO through photolysis, was detected in a chemiluminescence spectrometer by reaction with ozone (McMahon, T. J., and Stamler, J. S. (1999) Methods Enzymol. 301, 99-114).

[0180] Blood was obtained from the left ventricle (arterial) and jugular vein (venous) of anesthetized Sprague-Dawley rats: 12 were controls and 12 were treated with 100 mg/Kg of N-[4-(5-p-tolyl-3-trifluoromethyl-1H-pyrazol-1-yl)phenylsulfonyl]-p-nitroxymethylbenzamide (Ela). Red blood cells were isolated by centrifugation at 800 g, washed three times in phosphate buffered saline at 4 °C, lysed by the addition of 4-fold excess volume of deionized water containing 0.5 mM EDTA and desalted rapidly according to the method of Penefsky at 4 °C.

[0181] In 24 rats, Hb samples were divided in two aliquots which were then treated or not treated with 10-fold excess HgCl₂ which can remove the signal of Hb(Fel)NO.

[0182] N-[4-(5-p-tolyl-3-trifluoromethyl-1H-pyrazol-1-yl)phenylsulfonyl]-p-nitroxymethylbenzamide (Ela) can significantly increase S-nitrosohemoglobin (SNO-Hb) levels both in rat arterial and in rat venous blood.

TABLE III:

Endogenous S-nitrosohemoglobin (SNO-Hb) levels in rat blood and after administration of N-[4-(5-p-tolyl-3-trifluoromethyl-1H-pyrazol-1-yl)phenylsulfonyl]-p-nitroxymethylbenzamide (Ela)		
	Arterial SNOERR-Hb (nM)	Venous SNO-Hb (nM)
Endogenous levels	311 ± 55	32 ± 14
Levels after administration of (Ela) (100 mg/Kg i.p.)		

EXAMPLE 3

Arterial blood pressure effects of oral administration of sodium nitroprusside and (11β,16α)-9-fluoro-11,17-dihydroxy-21-(p-nitroxymethylbenzoyloxy)-pregna-1,4-diene-3,20-dione (ECXCa)

[0183] Sodium nitroprusside (0.5 mg/kg) in carboxymethylcellulose 0.5% or an equimolar dose (1.09 mg/Kg) of (11β,16α)-9-fluoro-11,17-dihydroxy-21-(p-nitroxymethylbenzoyloxy)-pregna-1,4-diene-3,20-dione (ECXCa) in carboxymethylcellulose 0.5% or the vehicle alone (control group) were administered per os to 15 male wistar rats divided into 3 groups and after anaesthesia.

[0184] Blood pressure was continuously recorded for 4 hours.

TABLE II:

RAT ARTERIAL BLOOD PRESSURE EFFECTS OF ORAL ADMINISTRATION OF SODIUM NITROPRUSSIDE (0.5 MG/KG) AND (11β,16α)-9-FLUORO-11,17-DIHYDROXY-21-(P-NITROXYMETHYLBENZOYLOXY)-PREGNA-1,4-DIENE-3,20-DIONE (ECXCA) (1.09 MG/KG)		
Control (%)	Sodium nitroprusside (%)	(ECXCa) (%)
100	76	100

[0185] These results prove that (11β,16α)-9-fluoro-11,17-dihydroxy-21-(p-nitroxymethylbenzoyloxy)-pregna-1,4-diene-3,20-dione (ECXCa) does not modify systemic blood pressure while sodium nitroprusside can cause a marked hypotension.

Claims

1. Compounds of general formula (I), their pharmaceutically acceptable salts, their in vivo hydrolyzable prodrugs, their tautomers and their diastereomers

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507, MEDI-517, MEN-10710, MEN-11066, MEN-11951, MER-1020DA, MER-WF1726, MG-132, MG98, MGI-114, MGv, MIBG, MK-4, MK571, MK-869, MK-886, MKT-077, MI-1544, MI-1892, MM-36, MMI-270, MPC-7869, M-PGA, MPI-5020, MPV-2213AD, MR-20492, MS-209, MS-247, MS-27-275, MS-275, MS-325, MSI-1857, MTP-PE, MUP-98176, MV9411, MX6, MT965-A, MT965-B, N276-15, NA-22598B1, NAMI-A, NB-506, NB-1011, NBI-3001, NC100150, NCA-0424, NCO-700, NF-062, NF-06307, NG-60, NK-611, NIK-250, NHTS, NLCQ-1, NM-3, NS-398, NSC-314622, NSC-330507, NSC-354258, NSC-614491, NSC-614491, NSC-649488, NSC-655649, NSC-658875, NSC-674495, NSC-676632, NSC-678515, NSC-686288, NSC-693569, NSC-693632, NSC-7103505, NSC-D699127, NU/ICRF-505, NU:UB-31, NU:UB-73, NU-2058, NU-3076, NU-3121, NV1020, NX-1838, NX-211, OC-1012, OC-144-093, ODN-2009, ODN-698, ODN-83, OGT-719, ON-5543, ONO-4007, ONO-8711, ONYX-015, ONYX-838, OPB-3206, ORI-1313, OSI-774, P-4055, PADP, PAM4, PAK-104, PAK-104P, PD-089828, PD-145709, PD-0174073, PD-0183812, PD-090560, PD-098059, PD-128763, PD-153035, PD-158780, PD-160878, PD-166285, PD-166866, PD-168393, PD-173074, PD-173955, PD-173956, PD-180970, PD-183805, PD-184352, PI-88, PI-CA91, PKC-412, PKI-166, PLQ-22, PNU 145156E, PNU-144113, PNU 153429, PNU-157914, PNU-157977, PNU-159548, PNU-166196, PNU-177496, PP-33, PR-39, PR-69, PRO-533, PS-341, PS-724, PS-990, PSC-833, PSP-94, PT-523, PT-624, PTK-787, PX12, P-X-1544, Q-85, QM16-A, QS-21, QW-1624F2-2, R-101933, R-109339, R115777, R-116010, R123942, RB94, RK-0202, RL-0903, RMP-7, RO-09-4889, RO-25-4020, RO-25-6760, RO-25-9716, RO-28-2653, RO-31-7453, RO-31-7453, RO-41-5253, RO-50-4258, RO-65-7674, RP-527, RPR-108518, RPR-108514A, RPR-109881, RPR-115781, RPR-116258A, RPR-130401, RSR13, S-1127, S-16020-2, S179D-PRL, S-20928, S-20929, S-23906-1, S-30372, S-30972-1, S-3304, S-8184, S-836, SAHA, SAM-484, SB 249553, SB-203580, SB-209763, SB-238039, SB-247464, SB-251353, SB-408075, SB 596168, SBAS2, SBR-11-2897, SBR-11-3702, SBR-170-, SB-RA-131012, SB-T-1213, SB-T-1250, SB-T-101187, SC-1, SC-68448, SC-72115, SC-AAD9, SCH-207758, SCH-56396, SCH-58500, SCH-66336, SCHL-705, SD-7, SGI-101, SGN-10, SGN-15, SH-207, SJG-136, SL11047, SL-11093, SN-38, SMT-487, SN-38, SNF-4435C, SQ-67454, SP-1053C, SPC8490, SPD-424, SPIKET-P, SR 2789, SR 27897, SR-271425, SR-271425-, SR29142, SR-29142, SR-45023A, SR-4895, SR-49059, SRL-172, SS-555, ST-1481, STA-BX909, STI-412, STI-481, STI-571, SU-0879, SU-101, SU-1433, SU-1498, SU4312, SU-4793, SU-4942, SU-4984, SU-5204, SU-5212, SU-5402, SU-5406, SU-5416, SU-5477, SU-5614, SU-6668, SU-9516, SU-9902, SW-163E, T12, T-138067, T-2591, T-3782, T-607, T-64, T-67, T-900607, T-904064, T-98475, TA-2516, TA-2620-, TAS-103, TAS106, TER-117, TER-199, TER-286, TG-1031, TIP-19.40, TJN-151, TLC-144, TLC-D-99, TLC-ELL-12, TLK-199, TLK286, TMC-169, TMC-96, TNP-470, TOP-53, TRK-710, TTNPB, TT-2, TT-232, TX-1123, TX-1920, TXD-258, TZT-1027, U-0126, UCN-01, UCS-1025A-, UCT-1072M1, V-93, VGA1102, VLTS-587, VN/85-1, VN/87-1, VNP-20009, VNP40101M, VP-16, VUF-5000, VUF-5434, VX-710, VX-853, WAY-170523, WHI-D11, WHI-D12, WHI-P154, WHI-P273, WIN-61651, WMC-26, WP-631, WP-745, WP-769, WR-1065, WT-126-34, WX-293T, XK-469, XR-11576, XR-3054, XR5000, XR-5944, XR-9576, YH-137, YH-138, YM294, YM511, YM529, YMB-6H9, ZD-0473, ZD-1626, ZD-1839, ZD-2767, ZD-4190, ZD-6126, ZD-6474, ZD-9063P, ZD-9331, ZK-119010, ZK-112993, ZK-191703, ZK-222584, ZK-229561, ZK-230211, ZM-445526, ZNPCF64, IRESSA, NEOQUIN

7. Compounds according to claims 1-6 in which -F is chosen among the following 8 groups of molecules (from 1 B to 8B) which are identified by their own structural formula or by their own INN ("International Nonproprietary Name" from "World Health Organization" database) or by their own company code or by their own chemical name.

GROUP 1B:

ABT-963, α -tocopherol, 8 α -hydroxy-riboflavin, aceclofenac, acemetacin, actarit, alciofenac, alclometasone, AGIX-4207, ajulemic acid (EL), amebucort, amelometasone, amiprilose, ampiroxicam, amtolmetin guacil, anakinra, anilolac, anisperimus, aprepitant, aspirin (ECI), AR-C73346XX (ECX), ataquimast (ECLX), atiprimod, atizoram, atreleuton, balsalazide (ECXVIII), bendazac, benorylate, benoxaprofen, benzydamine (ELX), bermoprofen, beclomethasone, betamethasone, betamethasone acibutate, bindarit, brequinar, BF-389 (EXLVIII), bromfenac, bucllamine, bucllamine, budesonide, bufexamac, bumadizone, butixocort, CB-2431, CC-1069, CC-1088, CEP-1347, celecoxib (EI) and 2 metabolites of it ((EII), (EIII)), chenodeoxycholic acid, chloroquine, ciclesonide, cinaproxen, cinmetacin, clidanac, clobuzarit, clofenamic acid, CGS-33090A, CLX-0921, CLX-120500, CK-135, COX-189, CS-502, cloticasone, CR-3558, cridanimod, cyclosporin A, darbufelone (EXLV), deflazacort, dehydrocholic acid, deltibant, deracoxib (EXIII), descinolone, desonide, dexamethasone (ECXC), dexketoprofen, dexamethasone acefurate, dexamethasone-21-phosphate, dexbudesonide, dexpemedolac, dextiopronin, diacerein, diclofenac (ECXIII), diflunisal, dipyrone, DPC-333, droxicam, erlotinib, esonarimod (XXXIV), etodolac (ECXVI), etofenamate, etoricoxib (EXI), E-5110 (EXLVI), everolimus, ezlopitant, fampridine (ELXI), felbinac, fenbufen, fenileuton, fentiazac, figopitant, flavine-adenine dinucleotide, flobufen (ECXVII), flosulide (EXXII), fluazacort, flufenamic acid, flunisolide, flurbiprofen (ECIV), fluticasone, fluocortin, FR-228352 (EVI), FTY-720 (ECL), ganaxolone, glucosamine (EXXX), ginkgolide B, GR-205171, GW-4459, halometasone, hydroxychloroquine, hydrocortisone (ECVIII), hyperin, ibufenac, ibuprofen (ECXIV), icatibant, ilonidap, indometacin (ECIX), indoprofen, ISIS-104838, isoxicam, ketopro-

EXAMPLE 2

Endogenous S-nitrosohemoglobin (SNO-Hb) levels in rat blood and after administration of N-[4-(5-p-tolyl-3-trifluoromethyl-1H-pyrazol-1-yl)phenylsulfonyl]-p-nitroxymethylbenzamide (Ela)

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	Arterial SNOERR-Hb (nM)	Venous SNO-Hb (nM)
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Levels after administration of (Ela) (100 mg/Kg i.p.)		

EXAMPLE 3

Arterial blood pressure effects of oral administration of sodium nitroprusside and (11β,16α)-9-fluoro-11,17-dihydroxy-21-(p-nitroxymethylbenzoyloxy)-pregna-1,4-diene-3,20-dione (ECXCa)

[0183] Sodium nitroprusside (0.5 mg/kg) in carboxymethylcellulose 0.5% or an equimolar dose (1.09 mg/Kg) of (11β,16α)-9-fluoro-11,17-dihydroxy-21-(p-nitroxymethylbenzoyloxy)-pregna-1,4-diene-3,20-dione (ECXCa) in carboxymethylcellulose 0.5% or the vehicle alone (control group) were administered per os to 15 male wistar rats divided into 3 groups and after anaesthesia.

[0184] Blood pressure was continuously recorded for 4 hours.

TABLE II:

RAT ARTERIAL BLOOD PRESSURE EFFECTS OF ORAL ADMINISTRATION OF SODIUM NITROPRUSSIDE (0.5 MG/KG) AND (11β,16α)-9-FLUORO-11,17-DIHYDROXY-21-(P-NITROXYMETHYLBENZOYLOXY)-PREGNA-1,4-DIENE-3,20-DIONE (ECXCA) (1.09 MG/KG)		
Control (%)	Sodium nitroprusside (%)	(ECXCa) (%)
100	76	100

[0185] These results prove that (11β,16α)-9-fluoro-11,17-dihydroxy-21-(p-nitroxymethylbenzoyloxy)-pregna-1,4-diene-3,20-dione (ECXCa) does not modify systemic blood pressure while sodium nitroprusside can cause a marked hypotension.

Claims

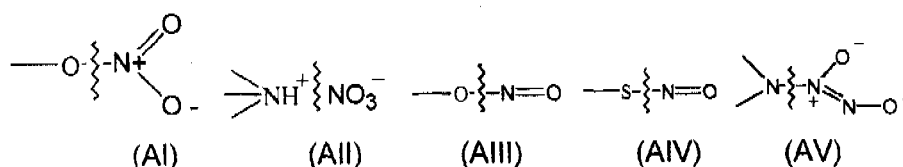
- Compounds of general formula (I), their pharmaceutically acceptable salts, their in vivo hydrolyzable prodrugs, their tautomers and their diastereomers



(I)

where:

- q is an integer from 1 to 5;
- F is a molecule or a drug for prevention and treatment of inflammatory, ischemic, degenerative and proliferative diseases of musculoskeletal, tegumental, respiratory, gastrointestinal, genito-urinary and central nervous systems;
- X is chosen among 3 groups of substituents, -M, -T and -V where:
 - M is chosen among the following groups which can release nitric oxide in vivo: nitrate ester (AI) -ONO₂; nitrate salt (AII); nitrite ester (AIII)
 - ONO; thionitrite (AIV) -SNO; NONOate (AV) -NO(NO)



- the undulated line shows where and how is the bond which is necessary to link M (on the right of the line) and the drug F (on the left of the line);
- T is chosen among the following radicals, optionally salified:
 - O-R₁-M; -O-R₁-O-R₁-M; -O-R₁-S-R₁-M; -O-R₁-NR₂-R₁-M;
 - S-R₁-M; -S-R₁-O-R₁-M; -S-R₁-S-R₁-M; -S-R₁-NR₂-R₁-M;
 - NR₂-R₁-M; -NR₂-R₁-O-R₁-M; -NR₂-R₁-S-R₁-M; -NR₂-R₁-NR₂-R₁-M;
 - (CO)-R₁-M; -(CO)-R₁-O-R₁-M; -(CO)-R₁-S-R₁-M; -(CO)-R₁-NR₂-R₁-M;
 - O-(CO)-R₁-M;
 - R₁-O-R₁-M; -R₁-S-R₁-M; -R₁-NR₂-R₁-M;
 - PO(O)-O-R₁-M;

where M is described as above;

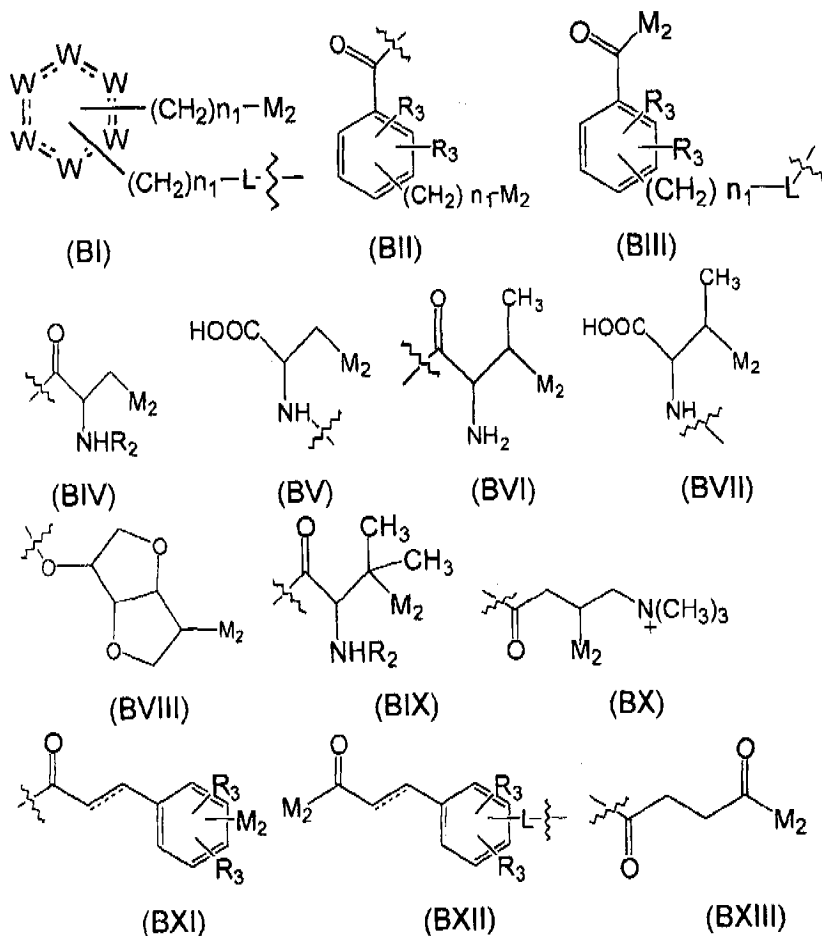
- R₁- is a saturated or unsaturated, linear or branched alkylene, having from 1 to 21 carbon atoms or a saturated or unsaturated, optionally heterosubstituted or branched cycloalkylene, having from 3 to 7 carbon atoms or an optionally heterosubstituted arylene having from 3 to 7 carbon atoms;
- R₂ is H or a saturated or unsaturated, linear or branched alkyl, having from 1 to 21 carbon atoms or a saturated or unsaturated, optionally heterosubstituted or branched cycloalkyl, having from 3 to 7 carbon atoms or an optionally heterosubstituted aryl having from 3 to 7 carbon atoms;
- R₁- and -R₂ may be substituted with -OH, -SH, -F, -Cl, -Br, -OPO₃H₂, -COOH, NR₂ or with a saturated or unsaturated, linear or branched alkyl, having from 1 to 10 carbon atoms or with a saturated or unsaturated, optionally heterosubstituted or branched cycloalkyl, having from 3 to 7 carbon atoms;
- the bond between -F and -T is hydrolyzable in vivo by metabolic or enzymatic activity and in particular is a carboxylic ester, a carboxylic amide, a glycoside, an acetal, a ketal, an azo compound, an hydrazide, a carbamate, a thioester, a thioamide, a phosphoric ester, a phosphonic ester, a sulphuric ester, a sulphonic amide, a sulphonic ester.
- the above cited pharmaceutically acceptable salts are salts from inorganic acid (e.g. nitrate, nitrite, chlorhydrate, bromhydrate, sulphate, phosphate), salts from organic acids (e.g. citrate tartrate, acetate, maleate, fumarate, ossalate, p-toluensulphonate, methanosulphonate, ethansulphonate, benzenesulphonate), from inorganic bases (e.g. ammonium, sodium, lithium, potassium, magnesium, calcium and zinc salts) or from organic bases (e.g. ammonium salts of organic amines).

The bond between -R₁ and -M is described by the above cited formulae from (AI) to (AV) that is the undulated line shows here where and how is the bond which is necessary to link -M (on the right of the line) and -R₁ (on the

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left of the line);

- V is chosen among $-Z-M_2$, $-O-Z-M_2$, $-N(R_2)-Z-M_2$, $-R_1-Z-M_2$, $-O-R_1-M_2$, $-O-R_1-Z-M_2$ where:
- M_2 is chosen among $-M$, $-R_1-M$, $-O-R_1-M$, $-S-R_1-M$, $-N(R_2)-R_1-M$
- where R_1 , R_2 and M are described as above;
- $Z-M_2$ is chosen among the following radicals, optionally salified with nitric acid:



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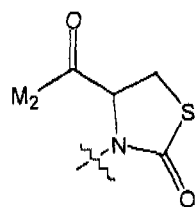
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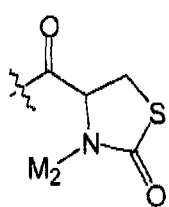
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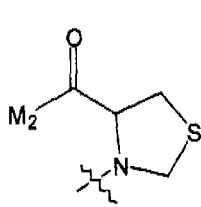
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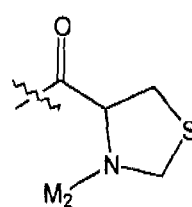
(BXIV)



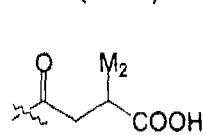
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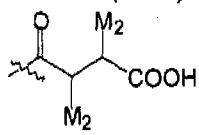
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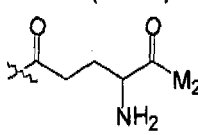
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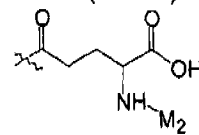
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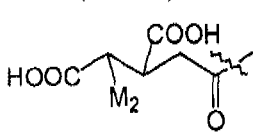
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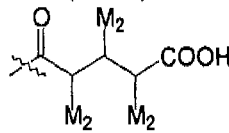
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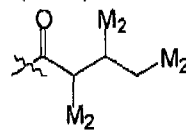
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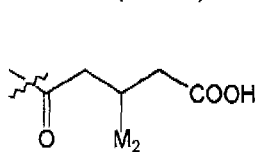
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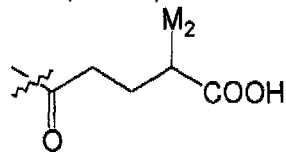
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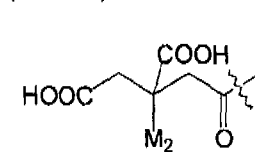
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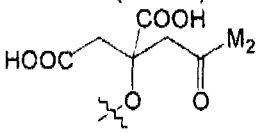
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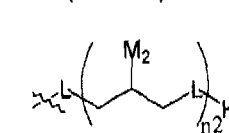
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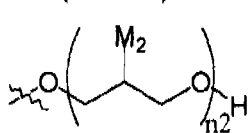
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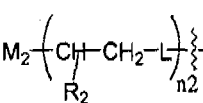
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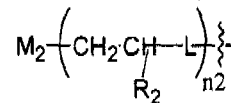
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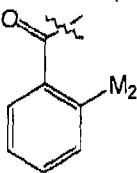
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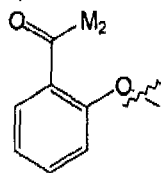
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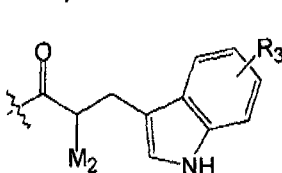
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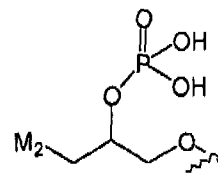
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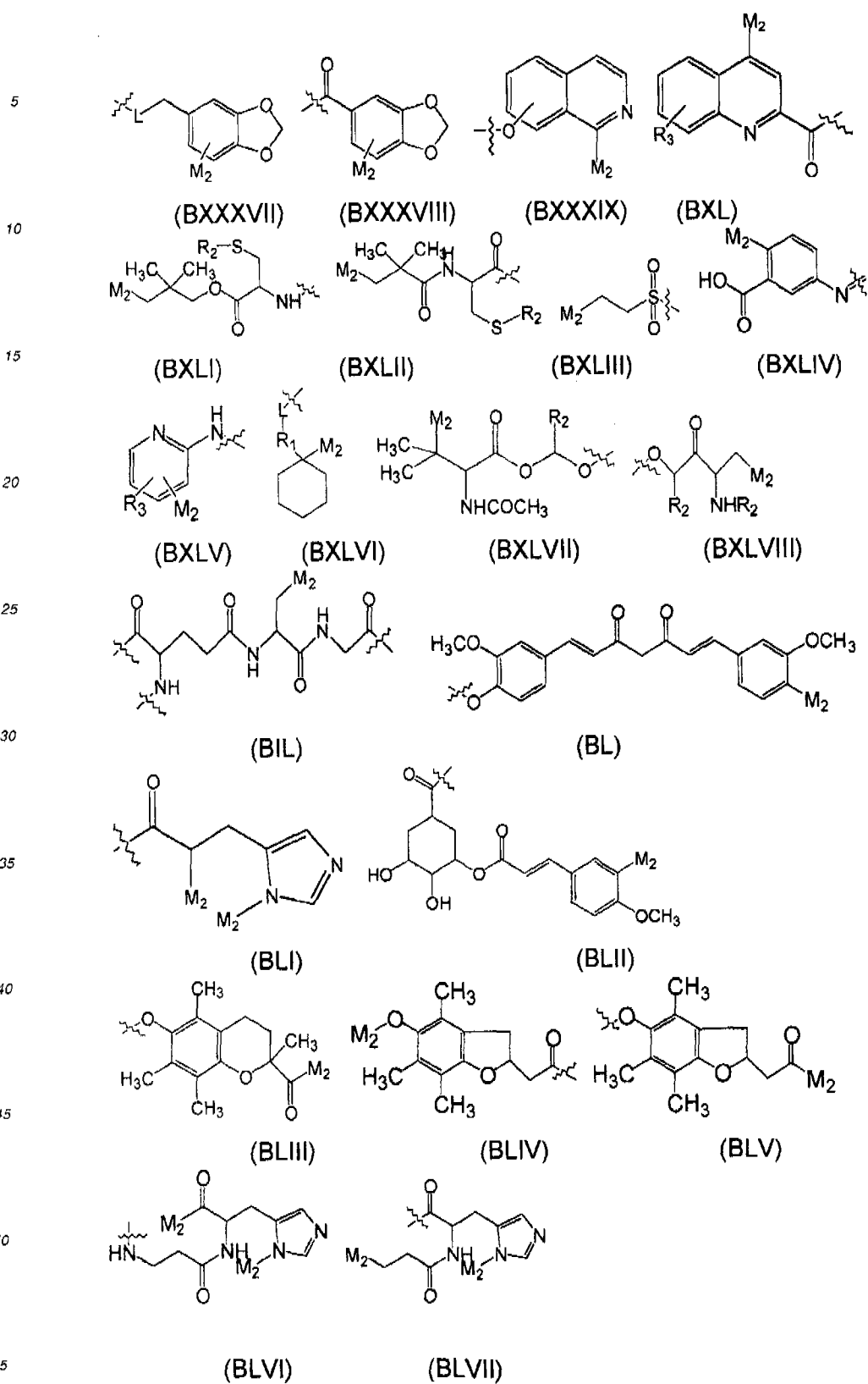


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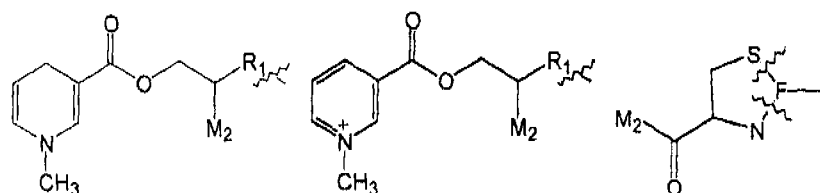


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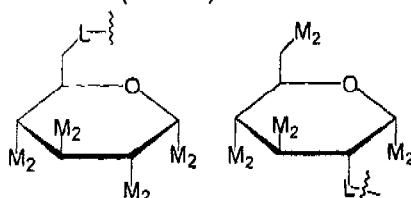
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(BLVIII)

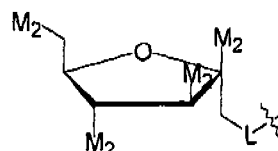
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(BLX)

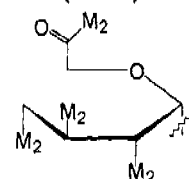


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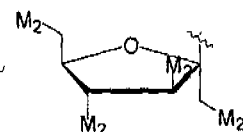
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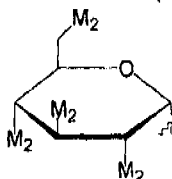
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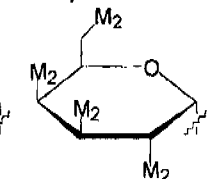
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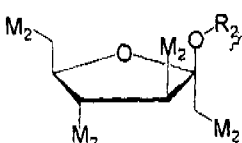
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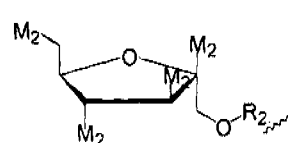
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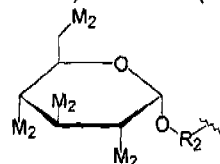
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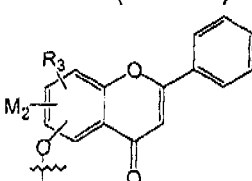
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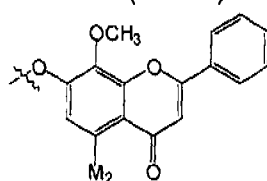
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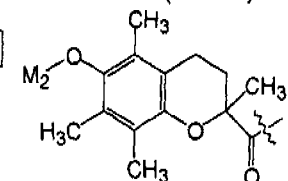
(BLXX)



(BLXXI)



(BLXXII)



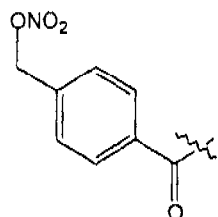
(BLXXIII)

where:

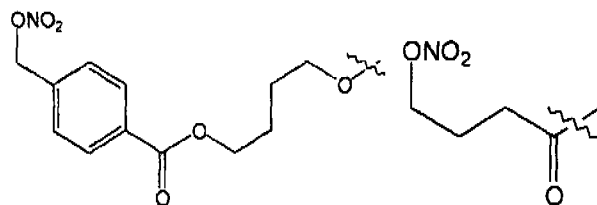
- R_3 is chosen among -H, -OH, -NH₂, -NO₂, -CH₃, -CN, -OCH₃, -CH₂OH, -COOH, -CHO, -F, -Cl, -Br, -CF₃;
- "L" is an oxygen atom -O-, a sulphur atom -S-, a nitrogen atom -NR₂-, a selenium atom -Se- or a carbon atom -CR₂R₂-;
- W is chosen among -CH=, =N-, -N+(O)=; n_1 is an integer from 0 to 3; n_2 is an integer from 1 to 6, preferably from 1 to 4;
- R_1 , R_2 , are described as above;
- the dotted line is a simple bond or a double bond; -Ar₁- is an optionally heterosubstituted arylene having from 3 to 7 carbon atoms;
- the undulated line shows where is the bond between -V and the drug -F;
- the bond between -F and -V is hydrolyzable in vivo by metabolic or enzymatic activity and in particular is a carboxylic ester, a carboxylic amide, a glycoside, an acetal, a ketal, an azo compound, an hydrazide, a car-

bammate, a thioester, a thioamide, a phosphoric ester, a phosphonic ester, a sulphonic amide, a sulphonic ester.

2. Compounds according to claim 1, in which -X is chosen among nitrate salt (All) in a stoichiometric ratio with F of at least 1:1 and the following monovalent radicals -Y₁ optionally salified with nitric acid:

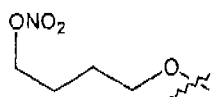


(CaI)

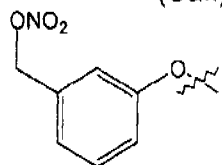


(CaII)

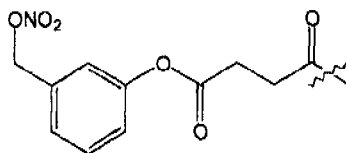
(CaIII)



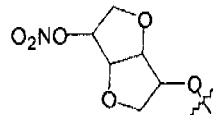
(CaIV)



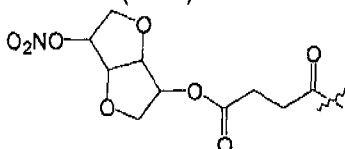
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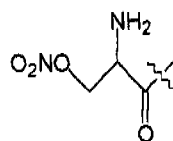
(CaVI)



(CaVII)



(CaVIII)



(CaIX)

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507, MEDI-517, MEN-10710, MEN-11066, MEN-11951, MER-1020DA, MER-WF1726, MG-132, MG98, MGI-114, MGv, MIBG, MK-4, MK571, MK-869, MK-886, MKT-077, MI-1544, MI-1892, MM-36, MMI-270, MPC-7889, M-PGA, MPI-5020, MPV-2213AD, MR-20492, MS-209, MS-247, MS-27-275, MS-275, MS-325, MSI-1857, MTP-PE, MUP-98176, MV9411, MX6, MT965-A, MT965-B, N276-15, NA-22598B1, NAMI-A, NB-506, NB-1011, NBI-3001, NC100150, NCA-0424, NCO-700, NF-062, NF-06307, NG-60, NK-611, NIK-250, NHTS, NLCO-1, NM-3, NS-398, NSC-314622, NSC-330507, NSC-354258, NSC-614491, NSC-614491, NSC-649488, NSC-655649, NSC-658875, NSC-674495, NSC-676632, NSC-678515, NSC-686288, NSC-693569, NSC-693632, NSC-7103505, NSC-D699127, NU/ICRF-505, NU:UB-31, NU:UB-73, NU-2058, NU-3076, NU-3121, NV1020, NX-1838, NX-211, OC-1012, OC-144-093, ODN-2009, ODN-698, ODN-83, OGT-719, ON-5543, ONO-4007, ONO-8711, ONYX-015, ONYX-838, OPB-3206, ORI-1313, OSI-774, P-4055, PADP, PAM4, PAK-104, PAK-104P, PD-089828, PD-145709, PD-0174073, PD-0183812, PD-090560, PD-098059, PD-128763, PD-153035, PD-158780, PD-160678, PD-166285, PD-166866, PD-168393, PD-173074, PD-173955, PD-173956, PD-180970, PD-183805, PD-184352, PI-88, PI-CA91, PKC-412, PKI-166, PLQ-22, PNU 145156E, PNU-144113, PNU 153429, PNU-157914, PNU-157977, PNU-159548, PNU-166196, PNU-177496, PP-33, PR-39, PR-69, PRO-533, PS-341, PS-724, PS-990, PSC-833, PSP-94, PT-523, PT-624, PTK-787, PX12, P-X-1544, Q-85, QM16-A, QS-21, QW-1624F2-2, R-101933, R-109339, R115777, R-116010, R123942, RB94, RK-0202, RL-0903, RMP-7, RO-09-4889, RO-25-4020, RO-25-6760, RO-25-9716, RO-28-2653, RO-31-7453, RO-31-7453, RO-41-5253, RO-50-4258, RO-65-7674, RP-527, RPR-108518, RPR-108514A, RPR-109881, RPR-115781, RPR-116258A, RPR-130401, RSR13, S-1127, S-16020-2, S179D-PRL, S-20928, S-20929, S-23906-1, S-30372, S-30972-1, S-3304, S-8184, S-836, SAHA, SAM-484, SB 249553, SB-203580, SB-209763, SB-238039, SB-247464, SB-251353, SB-408075, SB 596168, SBAS2, SBR-11-2897, SBR-11-3702, SBR-170-, SB-RA-131012, SB-T-1213, SB-T-1250, SB-T-101187, SC-1, SC-68448, SC-72115, SC-AAD9, SCH-207758, SCH-56396, SCH-58500, SCH-66336, SCHL-705, SD-7, SGI-101, SGN-10, SGN-15, SH-207, SJG-136, SL11047, SL-11093, SN-38, SMT-487, SN-38, SNF-4435C, SQ-67454, SP-1053C, SPC8490, SPD-424, SPIKET-P, SR 2789, SR 27897, SR-271425, SR-271425-, SR29142, SR-29142, SR-45023A, SR-4895, SR-49059, SRL-172, SS-555, ST-1481, STA-BX909, STI-412, STI-481, STI-571, SU-0879, SU-101, SU-1433, SU-1498, SU4312, SU-4793, SU-4942, SU-4984, SU-5204, SU-5212, SU-5402, SU-5406, SU-5416, SU-5477, SU-5614, SU-6668, SU-9516, SU-9902, SW-163E, T12, T-138067, T-2591, T-3782, T-607, T-64, T-67, T-900607, T-904064, T-98475, TA-2516, TA-2620-, TAS-103, TAS106, TER-117, TER-199, TER-286, TG-1031, TIP-19.40, TJN-151, TLC-144, TLC-D-99, TLC-ELL-12, TLK-199, TLK286, TMC-169, TMC-96, TNP-470, TOP-53, TRK-710, TTNPB, TT-2, TT-232, TX-1123, TX-1920, TXD-258, TZT-1027, U-0126, UCN-01, UCS-1025A-, UCT-1072M1, V-93, VGA1102, VLTS-587, VN/85-1, VN/87-1, VNP-20009, VNP40101M, VP-16, VUF-5000, VUF-5434, VX-710, VX-853, WAY-170523, WHI-D11, WHI-D12, WHI-P154, WHI-P273, WIN-61651, WMC-26, WP-631, WP-745, WP-769, WR-1065, WT-126-34, WX-293T, XK-469, XR-11576, XR-3054, XR5000, XR-5944, XR-9576, YH-137, YH-138, YM294, YM511, YM529, YMB-6H9, ZD-0473, ZD-1626, ZD-1839, ZD-2767, ZD-4190, ZD-6126, ZD-6474, ZD-9063P, ZD-9331, ZK-119010, ZK-112993, ZK-191703, ZK-222584, ZK-229561, ZK-230211, ZM-445526, ZNPCF64, IRESSA, NEOQUIN

7. Compounds according to claims 1-6 in which -F is chosen among the following 8 groups of molecules (from 1 B to 8B) which are identified by their own structural formula or by their own INN ("International Nonproprietary Name" from "World Health Organization" database) or by their own company code or by their own chemical name.

GROUP 1B:

ABT-963, α -tocopherol, 8 α -hydroxy-riboflavin, aceclofenac, acemetacin, actarit, alclofenac, alclometasone, AGIX-4207, ajulemic acid (EL), amebucort, amelometasone, amiprilose, ampiroxicam, amtolmetin guacil, anakinra, an-
irolac, anispermus, apreptant, aspirin (ECI), AR-C73346XX (ECX), ataquimast (ECLX), atiprimod, atizoram, atre-
leuton, balsalazide (ECXVIII), bendazac, benorylate, benoxaprofen, benzydamine (ELX), bermoprofen, beclom-
ethasone, betamethasone, betamethasone acibutate, bindarit, brequinar, BF-389 (EXLVIII), bromfenac, bucl-
llamine, bucllamine, budesonide, bufexamac, bumadizone, butixocort, CB-2431, CC-1069, CC-1088, CEP-1347,
celecoxib (EI) and 2 metabolites of it ((EII), (EIII)), chenodeoxycholic acid, chloroquine, ciclesonide, cinaproxen,
cinmetacin, clidanac, clobuzarit, clofenamic acid, CGS-33090A, CLX-0921, CLX-120500, CK-135, COX-189, CS-
502, cloticasone, CR-3558, cridanimod, cyclosporin A, darbufelone (EXLV), deflazacort, dehydrocholic acid, del-
tibant, deracoxib (EXIII), descinolone, desonide, dexamethasone (ECXC), dexketoprofen, dexamethasone ace-
furate, dexamethasone-21-phosphate, dexbudesonide, dexpemmedolac, dextiopronin, diacerein, diclofenac (ECX-
III), diflunisal, dipyrone, DPC-333, droxicam, erlotinib, esonarimod (XXXIV), etodolac (ECXVI), etofenamate, etor-
icoxib (EXI), E-5110 (EXLVI), everolimus, ezlopitant, fampridine (ELXI), felbinac, fenbufen, fenileuton, fentiazac,
figopitant, flavine-adenine dinucleotide, flobufen (ECXVII), flosulide (EXXII), fluazacort, flufenamic acid, flunisolide,
flurbiprofen (ECIV), fluticasone, fluocortin, FR-228352 (EVI), FTY-720 (ECL), ganaxolone, glucosamine (EXXX),
ginkgolide B, GR-205171, GW-4459, halometasone, hydroxychloroquine, hydrocortisone (ECVIII), hyperin,
ibufenac, ibuprofen (ECXIV), icatibant, ilonidap, indometacin (ECIX), indoprofen, ISIS-104838, isoxicam, ketopro-

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fen (ECXII), ketorolac (EXC), KME-4 (EXLVII), KE-758 (EXXXV), KE-748 (EXXXVI), LL-Z-1640-2, laquinimod,
 lanepitant, leflunomide (EXXV), limazocic, lobenzarit, L-745337 (EXX), lornoxicam, loteprednol, J-113863
 (ELXXX), meclofenamic acid, mesalazine (ECII), meloxicam (ECXV), methotrexate (ECC), 6-methoxy-2-naphthy-
 lacetic acid (ELXIV), mofetil, ML-3000 (EVIII), mizoribine, mivotilate, mofezolac, mometasone, moxilubant, myc-
 5 ophenolate mofetil (EXXVIII), mycophenolic acid (EXXIX), MX-68 (EC), nabumetone, naflocort, naproxen (ECV),
 N-desmethylbenzylamine (ELXIII), nepadutant, nepafenac, niflumic acid, nimesulide (EXV), NS-398 (EXXXIII),
 olsalazine, oxaprozin, oxolamine, oxisopred, paracetamol (ECVI), paramethasone, parecoxib (EIV), pemedolac,
 penicillamine, pentostatin, pimecrolimus, piroxicam, PNU-156804, pralnacasan (EXXXVII), prasterone (ECLXII),
 prifelone, prednisone, prednisolone (ECVII), prednazoline (ECCI), propacetamol, proglumetacin, quercetin, rem-
 10 inertant, resiquimod, rhein, riboflavin, riboflavin monophosphate, riboflavin tetrabutylate, riboflavin triacetate,
 ridogrel (ECXL), rimonabant, rofecoxib (EIX), romazarit, rofleponide, roquinimex (ECLXI), RWJ-67657, RWJ-
 68354, salicylic acid (ECXCI), S-19812 (ECXXX), SB-202190, SB-203580, SB-220025, SCIO-469, sinomenine,
 sirolimus, sivelestat, solimastat, SP-600125, spiradolene, sulfasalazine, S-2474 (EXXVII), SU-5271 (ELXII), sulin-
 dac (ECXI), suprofen, suxibuzone, tacrolimus, talnetant, tanomastat, tauroselcholic acid, tazofelone, tazadolene,
 15 tebufelone (ECXXXI), tenidap (ECIII), tenoxicam, tepoxalin (EVII), teriflunomide (EXXIV), thalidomide, tiaramide,
 ticolubant, tifurac, tilmacoxib (EIV), tilnoprofen arbamel, tiopronin, tomoxiprole, tolfenamic acid, tresperimus, T-
 614 (EXXI), TBC-1269, TSL-225, TTL-3, triamcinolone, triptolide, ursulcholic acid, UR-8813, ursodiol (ELXV) (EgX-
 II), valdecoxib (EV), vofopitant, VX-745, WHI-P131 (ECLI), Y-39041, zileuton (ECXX), zomepirac, (EX), (EXII),
 (EXVI), (EXVII) (EXVIII), (EXIX), (EXXI-b), (EXXXI), (EXXXII), (EXXXIII), (ELXX), (EXXXVIII), (EXXXIX), (EXL),
 20 (EXLI), (EXLII) (ECLXIII), (ECLXX) (ECLXXI), (ECLXXII), (ECLXXX), (ECLXXXI), (ECLXXXII) (ECLXXXIII),
 (ECLXXXIV), (ECLXXXV), (ECLXXXVI)

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

2020
Bogotá, D.C.,

Doctor
ALVARO CORREA ORDOÑEZ
Apoderado

ASUNTO	Radicación	06-101178
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	3999
	Folios	002

Como resultado del examen de búsqueda de anterioridades y con fundamento en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. SOLICITUD DE SUMINISTRO DE INFORMACIÓN

El artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: "La Oficina Nacional competente podrá requerir el informe de expertos o de organismos científicos o tecnológicos que se consideren idóneos, para que emitan opinión sobre la patentabilidad de la invención. Asimismo, cuando lo estime conveniente, podrá requerir informes de otras oficinas de propiedad industrial. De ser necesario, a efectos del examen de patentabilidad y a requerimiento de la oficina nacional competente, el solicitante proporcionará, en un plazo que no excederán de 3 meses, uno o más de los siguientes documentos relativos a una o más de las solicitudes extranjeras referidas total o parcialmente a la misma invención que se examina: ... b) copia de los resultados de exámenes de novedad o de patentabilidad efectuados respecto a esa solicitud extranjera; ... Si el solicitante no presentara los documentos requeridos dentro del plazo señalado en el presente artículo la oficina nacional competente denegará la patente".

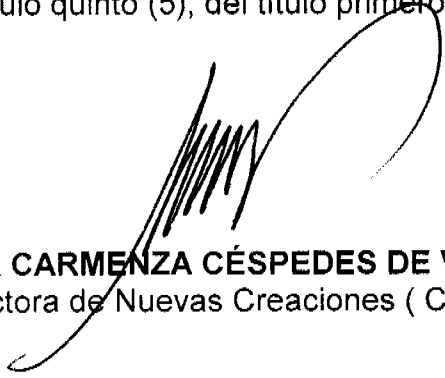
Como consecuencia de la búsqueda de anterioridades de materia relacionada con la de la presente invención, se determinó que existen en el estado de la técnica los siguientes documentos, que eventualmente afectarían los requisitos de patentabilidad de esta solicitud:

- LEUNER CHRISTIAN ET AL : « Improving drug solubility for oral delivery using solid dispersions » EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, ELSEVIER SCIENCE PUBLISHERS B.V., AMSTERDAM, NL, vol. 50, no.1, July 2000, pages 47-60, XP002155099 ISSN : 0939-6411
- PASSERINI NADIA ET AL : « preparation and characterisation of ibuprofen-poloxamer 188 granules obtained by melt granulation. « EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES : OFFICIAL JOURNAL OF THE EUROPEAN FEDERATION FOR PHARMACEUTICAL SCIENCES. FEB 2002, vol .15, no. 1, february 2002, pages 71-78, XP002334089 ISSN : 0928-0987

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Siendo que las publicaciones referenciadas hacen parte del resultado del examen de búsqueda realizado para la solicitud WO equivalente a esta solicitud colombiana aquí estudiada, y no siendo viable la consecución de dichos artículos por este despacho, se requiere que el solicitante, en virtud de lo establecido en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, proporcione las publicaciones completas, con lo que podrá realizarse un análisis absoluto de la patentabilidad de la invención correspondiente a la presente solicitud.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto (5), 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 19 MAR. 2010

CONCEPTO TÉCNICO Nº: 508	EXAMINADOR TÉCNICO Código N°: 202087	EXAMINADOR JURÍDICO Código N°:
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
ALVARO CORREA ORDOÑEZ
Apoderado

ASUNTO	Radicación	06-101178
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	3998
	Folios	117

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☒
		Cap. II	☐
No. Sol. Internacional	PCT/US2005/011678		
Fecha de Presentación Internal.	2005/04/07		

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

1. Documentos estudiados

Descripción: Folios: 18 a 43

Reivindicaciones: Folios 43 a 48 como se radicó inicialmente

Prioridad: Fecha: 2004/04/08, país: US y número: 60/560.452

2. Objeto de la invención

- Título de la solicitud: Formulaciones de dispersiones solidas de acetato de bazedoxifeno y número de folio: 1

El problema planteado en esta solicitud es la necesidad de formulaciones de bazedoxifeno que muestren biodisponibilidad mejorada en comparación con el bazedoxifeno cristalino o microcristalino para permitir dosificación mas baja.

Para solucionar este problema técnico la solicitud en estudio proporciona dispersiones sólidas y composiciones del modulador selectivo de estrógenos ácido 1-[4-(2-azepan-1-il-etoxi)-bencil]-2-(4-hidroxifenil)-3-metil- 1H-indol-5-ol acético es decir, acetato de bazedoxifeno.

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3. De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

Una vez revisado el capítulo reivindicatorio esta dependencia encuentra:

- Reivindicaciones 14 - 16: Se está caracterizando una dispersión sólida por su solubilidad en equilibrio en ácido acético o su AUC₀₋₂₄, C_{max}, t_{max}, lo cual es inaceptable ya que son los resultados a esperar o las ventajas de la misma por lo tanto no son las características esenciales de la dispersión que se pretende reivindicar.
- Reivindicaciones 8 – 12: Se reivindican relaciones de principio activo:agente de dispersión que no se han evaluado mediante ensayos, se requiere al solicitante restringir a lo que verdaderamente ha probado tener efectos ventajosos.

4. Excepción a la patentabilidad (artículo 20 D486 literal a)-d)

Reivindicación 35-41: Se refiere a un método para tratar a un mamífero por lo tanto están exceptuadas de patentabilidad según la legislación vigente.

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

Reivindicación 42: Se refieren a usos de las dispersiones sólidas para la fabricación de medicamentos por lo tanto están exceptuadas de patentabilidad según la legislación vigente

6. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 2004/04/08

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D ₁	EP 1336602	Nitrate prodrugs able to release nitric oxide in a controlled and selective way and their use for prevention and treatment of inflammatory, ischemic and proliferative diseases	2003/08/20

7. Análisis de patentabilidad (artículo 14 D486)

Novedad (artículo 16 D486)

Reivindicación 1: Una dispersión sólida que comprende acetato de bazedoxifeno disperso en un agente de dispersión.
Reivindicación 26: Composición que comprende una dispersión sólida reivindicada y un vehículo.
Reivindicación 32: forma de dosificación que comprende la dispersión sólida reivindicada.

D₁ enseña formulaciones de dispersión sólida entre las cuales están las que contienen el principio activo bazedoxifeno en forma amorfizada completa o parcial cuyo fin es mejorar la biodisponibilidad y la solubilidad, este principio activo se encuentra disuelto en un agente de dispersión como un alcohol y además contiene la polivinilpirrolidona como excipiente para resultar en formas farmacéuticas como tabletas o cápsulas.

- ♦ Tres (3) de los elementos característicos de la composición de la reivindicación 1, es decir: **una dispersión sólida, con acetato de bazedoxifeno y un agente de dispersión** habían sido divulgados previamente en el Estado de la Técnica según la tabla siguiente:

TABLA 1	
CARACTERÍSTICAS REIVINDICADAS	D ₁
dispersión sólida	Si Folio 99 ln 17
acetato de bazedoxifeno	Si Folios 98 [0046]
agente de dispersión	Si Folios 99, ln 15

De manera que el objeto de esta solicitud, tal como aparece en las reivindicaciones 1 - 16, no es nuevo, así como tampoco sería nueva la composición que contiene tal dispersión sólida según la reivindicaciones 26 – 31 y tampoco la forma de dosificación que contiene tal dispersión sólida según las reivindicaciones 32 - 34.

Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica:

- Reivindicación 17: Método para preparar la dispersión sólida que comprende:
- a) combinar acetato de bazedoxifeno y dicho agente de dispersión en solución, que tiene un solvente (solvente orgánico: alcohol)
 - b) Remover dicho solvente para producir la dispersión sólida
- Reivindicación 22: Método para preparar la dispersión sólida que comprende:

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- a) combinar acetato de bazedoxifeno con agente de dispersión fundido para formar una mezcla líquida
 - b) solidificar dicha mezcla líquida para formar la dispersión sólida
- Reivindicación 25: una dispersión sólida preparada por uno de los métodos reivindicados.

Dichos métodos están afectados por el siguiente documento del Estado de la Técnica:

D₁ enseña formulaciones de dispersión sólida entre las cuales están las que contienen el principio activo bazedoxifeno en forma amorfizada completa o parcial cuyo fin es mejorar la biodisponibilidad y la solubilidad, este principio activo se encuentra disuelto en un agente de dispersión como un alcohol y además contiene la polivinilpirrolidona como excipiente para resultar en formas farmacéuticas como tabletas o cápsulas.

La única **diferencia con D₁** es que esta solicitud **menciona 2 pasos en cada técnica "combinar y remover" o "combinar y solidificar"** pero esta diferencia no parece conceder un efecto técnico inesperado.

No puede determinarse un efecto técnico que logre la diferencia con la anterioridad encontrada porque la descripción no presenta datos en tal sentido.

El problema técnico objetivo de la invención podría redefinirse en: "como lograr métodos alternativos para la preparación de dispersiones sólidas con bazedoxifeno".

Por tanto, la solicitud, tal como se reivindica, es obvia, porque el experto medio en la materia enfrentado al problema de lograr métodos alternativos para la preparación de dispersiones sólidas con bazedoxifeno y conociendo el estado de la técnica haría lo que dice en D₁ ya que las técnicas de dispersión sólida ya eran conocidas a partir de dicha anterioridad, en donde se amortizan los compuestos mediante liofilización, amasamiento o preferiblemente secado en spray y comolienda. En D₁ ya se describía entonces como se disuelve un principio activo en un solvente, por ejemplo alcohol y así se obtiene una solución que es mezclada a temperatura ambiente con una solución o una suspensión de excipientes capaces de amortizar los principios activos. Por lo tanto, es una labor rutinaria para un experto medio en la materia preparar una dispersión sólida para mejorar la solubilidad y la biodisponibilidad, usando polímeros bien conocidos tales como PVP, poloxamero o PEG en varias posibilidades de relaciones entre el principio activo y el polímero y de esta manera logra fácilmente lo reivindicado.

En conclusión, no se considera que la presente solicitud merezca reconocimiento de nivel inventivo.

6. Conclusión:

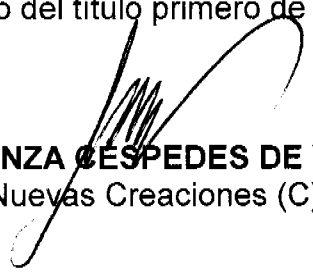
Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D ₁	EP1336602	1-16, 26-34 17-25	NOVEDAD NIVEL INVENTIVO

117 117 117
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En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 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

19 MAR. 2018

CONCEPTO TÉCNICO No. 508	EXAMINADOR TÉCNICO Código No. 202087
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