

LLOREDA & CIA. S. A.

ABOGADOS

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 03-027152- -00006-0002

Fecha: 2008-08-21 16:54:21
Tra. 11 PATENTEYII
Act. 411 PRESENTACION

Dep. 2020 NUECREACION
Eve: 344 DESGLOSE
Folios: 2

252
A - COLOMBIA
FUNDADA EN 1941
JO AEREO 12304
3264270 57-1-6069700
3264271 57-1-6069701
S: LLOREDA
2 No. 5-83 5º. PISO

www.lloredacamacho.com

jllcco@lloredacamacho.com

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: P1.-JANSSEN PHARMACEUTICA N.V.-Solicitud de Patente de
Invención en Fase Nacional PCT para "POLIARILCARBOXAMIDAS
ÚTILES COMO AGENTES REDUCTORES DE LÍPIDOS".-Clase C07D
211/34.-Expediente número 03-027.152.-

1. Me refiero a mi memorial de 19 de Agosto de 2008.
2. Dando alcance a dicha comunicación, me permito presentar recibo número **08 - 63,539** por valor de **\$103.000.00**, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de las modificaciones presentadas, ya que por un error involuntario se presentó un recibo por valor de **\$501.000.00**.
3. En vista de lo anterior, solicito a usted muy comedidamente se efectúe el desglose del recibo número 08 - 63,590 expedido por la Superintendencia de Industria y Comercio.
4. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,

ALICIA LLOREDA RICAURTE
T.P. 53.215

253

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 63,539
FECHA : AGOSTO 11 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 03-027152- -00006-0002

Fecha: 2008-08-21 16:54:21 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 344 DESGLOSE
Act. 411 PRESENTACION Folios: 2

**** CONSIGNACION ****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLOREDA Y CIA S. A	CONSIGNACION	BANCO DE BOGOTA	062754387	86293616	11/08/2007	10,128,000.00

**** CONCEPTO ****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12 MARCAS Y LEMAS COMERCIALES	103,000.00
		TOTAL :	\$ 103,000.00

SON: CIENTO TRES MIL PESOS

RESPONSABLE : _____

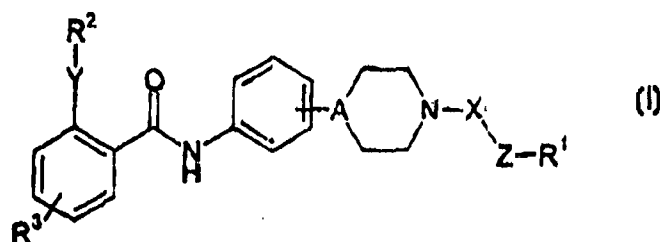
RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 295/155, 295/135, A61K 31/445, 31/495, A61P 3/06, 9/10		(11) International Publication Number: WO 00/32582
A1		(43) International Publication Date: 8 June 2000 (08.06.00)
(21) International Application Number: PCT/EP99/09320		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, 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, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 1 December 1999 (01.12.99)		
(30) Priority Data: 9826412.0 3 December 1998 (03.12.98) GB		
(71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).		
(72) Inventor; and (75) Inventor/Applicant (for US only): DAUGAN, Alain, Claude-Marie [FR/FR]; Laboratoire Glaxo Wellcome, Centre de Recherches, ZA de Courtaboeuf, 25, avenue de Québec, F-91940 Les Ulis (FR).		
(74) Agent: LEAROYD, Stephanie, Anne; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: BENZAMIDE DERIVATIVES AND THEIR USE AS APOB-100 SECRETION INHIBITORS



(57) Abstract

The invention relates to therapeutic benzamide compounds of formula (I) wherein A represents N or CH; X is selected from the following groups: (i) -C₁₋₆alkylene-, optionally containing one or two double bonds and optionally substituted by one or more hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ acyl or C₁₋₆ acyloxy groups, (ii) oxo, sulfonyl, thioxo, (iii) -C₁₋₆alkylenecarbonyl-, -C₁₋₆alkylenesulfonyl-, -C₁₋₆alkylenethioxo-, (iv) -C₂₋₆alkylenethio-, -C₂₋₆alkylenethio-, -C₂₋₆alkylene(N-H or N-C₁₋₆alkyl)amino-, (v) -C₁₋₆alkylenecarboxy-, -C₁₋₆alkylenethioamido-, -C₁₋₆alkylene(N-H or N-C₁₋₆alkyl)carboxamido-, and (vi) -C₂₋₆alkylenecarboxamido-, -C₂₋₆alkylenecarboxyl-, -C₂₋₆alkylene(N-H or N-C₁₋₆alkyl)aminocarbonyl-; Z represents a direct link or -C₁₋₆alkylene-, optionally containing one double bond and optionally substituted by one or more hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ acyl or C₁₋₆ acyloxy groups; R¹ is selected from the following groups: (i) hydrogen, C₁₋₃perfluoroalkyl, (ii) C₆₋₁₀ aryl, C₃₋₈cycloalkyl and fused benz derivatives thereof, C₇₋₁₀polycycloalkyl, C₄₋₈cycloalkenyl, C₇₋₁₀polycycloalkenyl, (iii) a heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, and (iv) where either X is C₁₋₆alkylene and Z is a direct link, or Z is C₁₋₆alkylene; R¹ additionally may represent a halogen, cyano, nitro or C₁₋₆acyl group, wherein, when R¹ contains one or more rings, said rings may each independently bear 0 to 4 substituents. Y represents a direct or oxy link, -C₁₋₆alkylene-, -oxyC₁₋₆alkylene- or a heterocyclyl consisting of monocyclic radicals. R² represents phenyl, C₃₋₈cycloalkyl, or a heterocyclyl consisting of monocyclic radicals, and where each R² is optionally substituted by one or more groups independently selected from halogen, C₁₋₄alkyl, C₁₋₄alkoxy, C₃₋₈cycloalkyl, C₁₋₃perfluoroalkyl, C₁₋₄perfluoroalkoxy, hydroxycarbonyl, C₁₋₆alkoxycarbonyl, cyano, nitro, C₁₋₄alkylaminosulfonyl; R³ represents hydrogen or one or more groups independently selected from halogen, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₃perfluoroalkyl or C₁₋₃perfluoroalkoxy; or a physiologically acceptable salt, solvate or derivative thereof, pharmaceutical compositions, to processes for their preparation and their use in the treatment of conditions mediated by ApoB-100 regulation.

m.p. : 120°C.

Example 88

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [4-[4-(3-cyano-benzyl)-piperazin-1-yl]-phenyl]-amide hydrochloride salt

To a solution of 4'-trifluoromethyl-biphenyl-2-carboxylic acid [4-[4-(3-cyano-benzyl)-piperazin-1-yl]-phenyl]-amide (0.2 g) in AcOEt (25 mL) was added 1N hydrochloric acid (0.9 mL) and the resulting solution was stirred at room temperature for 1.5 hours. The solution was then evaporated to dryness and the solid was recrystallized from AcOEt/hexane to give the title compound (0.18 g) as a white powder.

m.p. : 165°C.

Biological Assay

Primary human hepatocytes were seeded at 50 000 cells/well in 96 well plates. After an overnight adhesion phase, cells were incubated with compounds for 8 hours in RPMI medium containing 1% FCS, 4 µg/ml insulin, 100 nM dexamethasone and 50 µCi/ml ³⁵S-methionine. Compounds were dissolved in DMSO and tested onto cells from 1 µM to 1.6 nM. Production of radiolabeled apoB-100 and apoA-1 (used as a selectivity control) was quantified by analysis of supernatants using SDS PAGE and exposure of gels onto PhosphorImager screens. Inhibition of apoB-100 and apoA-1 secretion by compounds was calculated taking untreated cells as controls, and IC₅₀ of each compound was determined on both apoproteins. The following results were obtained for a selection of compounds of the invention:

Example no.	Primary human hepatocytes IC ₅₀ (nM)
1	13
3	18
63	20
4	12
3	13
62	10

68

2	18
6	18
64	19
5	15

Tablet compositions

The following compositions A and B can be prepared by wet granulation of ingredients (a) to (c) and (a) to (d) with a solution of povidone, followed by addition of the magnesium stearate and compression.

Composition A

		<u>mg/tablet</u>	<u>mg/tablet</u>
	(a) Active ingredient	250	250
10	(b) Lactose B.P.	210	26
	(c) Sodium Starch Glycollate	20	12
	(d) Povidone B.P.	15	9
	(e) Magnesium Stearate	<u>5</u>	<u>3</u>
		500	300

Composition B

		<u>mg/tablet</u>	<u>mg/tablet</u>
	(a) Active ingredient	250	250
	(b) Lactose 150	150	-
20	(c) Avicel PH 101	60	26
	(d) Sodium Starch Glycollate	20	12
	(e) Povidone B.P.	15	9
	(f) Magnesium Stearate	<u>5</u>	<u>3</u>
		500	300

Composition C

	<u>mg/tablet</u>
Active ingredient	100
Lactose	200
30 Starch	50
Povidone	5