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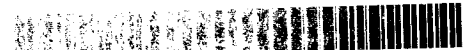
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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-090931.-00005-0000

Dep. 2020 NUECREACIONES
Eve: 379 FASENACIONALII
Folios: 2

Re: P1.-BANYU PHARMACEUTICAL CO., LTD.-Solicitud de Patente de
Invención en Fase Nacional PCT para "NOVEDOSOS DERIVADOS
DE 2-PIRIDINCARBOXAMIDA".-Clase C07D 401/14.-Expediente
número 05-090.931.-

1. Me refiero a mi memorial de 11 de Mayo de 2006.
2. De conformidad con lo dispuesto en el Artículo 5.2.12 de la Circular Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial número **576** de 31 de Mayo de 2007, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente invención.
3. Me permito recordar a usted, que tal como se informó en el Petitorio de la invención, la presente solicitud corresponde a Capítulo II.
4. Anexo me permito acompañar recibo número 07-82.445, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa que dicho examen causa.

Señor Superintendente,

ALICIA LLOREDA RICAURTE

T.P. 53.215

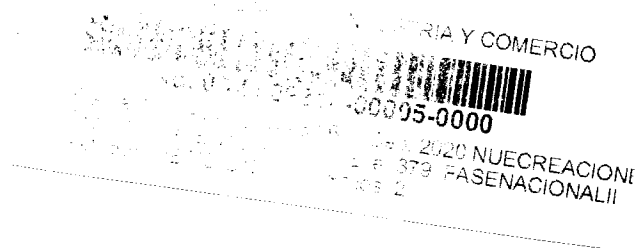
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 82,445
FECHA : OCTUBRE 8 DE 2007



***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLOREDA Y CIA S. A	CONSIGNACION	BANCO POPULAR	050-00110-6	47999513	08/10/2007	10,026,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILID	202,000.00
		TOTAL :	\$ 202,000.00

SON: DOSCIENTOS DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISION DE NUEVAS CREACIONES

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RADICACIÓN EXPEDIENTE No 05-90931

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **576** DE

FECHA **31 DE MAYO DE 2007** EL TERMINO HABIL SEÑALADO POR LA LEY

EXPIRA EL **31 DE AGOSTO DEL 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) World Intellectual Property Organization
International Bureau(43) International Publication Date
3 January 2003 (03.01.2003)

PCT

(10) International Publication Number
WO 03/000267 A1(51) International Patent Classification: A61K 31/496,
31/506, 31/443, 31/5377, 31/436, 31/4439, C07D 213/80,
413/12, 417/12, 401/12, 417/14, 405/12, 409/14

(21) International Application Number: PCT/GB02/02873

(22) International Filing Date: 24 June 2002 (24.06.2002)

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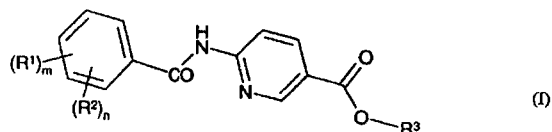
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Cheshire SK10 4TG (GB).(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MY, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
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GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
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Published:

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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: AMINO NICOTINATE DERIVATIVES AS GLUCOKINASE (GLK) MODULATORS

(57) Abstract: The invention related to novel compounds of Formula (I) or a salt, solvate or prodrug thereof, wherein R¹, R₂, R₃, n and m are as described in the specification, useful in the treatment of a (A chemical formula should be inserted here - please see paper copy enclosed) Formula (I) disease or condition mediated through glucokinase (GLK), such as type 2 diabetes. The invention also relates to methods for preparing compounds of Formula (I) and their use as medicaments in the treatment of diseases mediated by glucokinase.

AMINO NICOTINATE DERIVATIVES AS GLUCOKINASE (GLK) MODULATORS

The present invention relates to compounds which activate glucokinase (GLK), leading to a decreased glucose threshold for insulin secretion. In addition the compounds are predicted to lower blood glucose by increasing hepatic glucose uptake. Such compounds may have utility in the treatment of Type 2 diabetes and obesity. The invention also relates to pharmaceutical compositions comprising a compound of the invention, and use of such a compound in the conditions described above.

In the pancreatic β -cell and liver parenchymal cells the main plasma membrane glucose transporter is GLUT2. Under physiological glucose concentrations the rate at which GLUT2 transports glucose across the membrane is not rate limiting to the overall rate of glucose uptake in these cells. The rate of glucose uptake is limited by the rate of phosphorylation of glucose to glucose-6-phosphate (G-6-P) which is catalysed by glucokinase (GLK) [1]. GLK has a high (6-10mM) K_m for glucose and is not inhibited by physiological concentrations of G-6-P [1]. GLK expression is limited to a few tissues and cell types, most notably pancreatic β -cells and liver cells (hepatocytes) [1]. In these cells GLK activity is rate limiting for glucose utilisation and therefore regulates the extent of glucose induced insulin secretion and hepatic glycogen synthesis. These processes are critical in the maintenance of whole body glucose homeostasis and both are dysfunctional in diabetes [2].

In one sub-type of diabetes, Type 2 maturity-onset diabetes of the young (MODY-2), the diabetes is caused by GLK loss of function mutations [3, 4]. Hyperglycaemia in MODY-2 patients results from defective glucose utilisation in both the pancreas and liver [5]. Defective glucose utilisation in the pancreas of MODY-2 patients results in a raised threshold for glucose stimulated insulin secretion. Conversely, rare activating mutations of GLK reduce this threshold resulting in familial hyperinsulinism [6, 7]. In addition to the reduced GLK activity observed in MODY-2 diabetics, hepatic glucokinase activity is also decreased in type 2 diabetics [8]. Importantly, global or liver selective overexpression of GLK prevents or reverses the development of the diabetic phenotype in both dietary and genetic models of the disease [9-12]. Moreover, acute treatment of type 2 diabetics with fructose improves glucose tolerance through stimulation of hepatic glucose utilisation [13]. This effect is believed to be mediated through a fructose induced increase in cytosolic GLK activity in the hepatocyte by the mechanism described below [13].

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each Y is independently selected from phenyl(CH₂)₀₋₂, naphthyl(CH₂)₀₋₂,

heterocyclyl(CH₂)₀₋₂, C₃₋₇ cycloalkyl(CH₂)₀₋₂, C₁₋₆alkyl, C₂₋₆alkenyl or C₂₋₆alkynyl;

and each Y is independently optionally substituted by R⁴;

each R⁴ is independently selected from halo, CH₃₋₃F_a, CN, NO₂, NH₂, C₁₋₆alkyl,

5 OC₁₋₆alkyl, COOH, C(O)OC₁₋₆alkyl, OH, phenyl,

or R⁵-X¹-, where X is independently as defined for X above, and R⁵ is selected from hydrogen, C₁₋₆alkyl, CH₃₋₃F_a, phenyl, naphthyl, heterocyclyl or C₃₋₇cycloalkyl;

and R⁵ is optionally substituted by halo, C₁₋₆alkyl, -CH₃₋₃F_a, CN, NO₂, NH₂, COOH and -C(O)OC₁₋₆alkyl;

10 each a is independently 1, 2 or 3;

R³ is selected from hydrogen or C₁₋₆alkyl.

with the proviso that:

(i) when R³ is hydrogen or methyl, m is 1 and n is 0 then R¹ cannot be halo or methyl;

(ii) when R³ is hydrogen or methyl, m is 2 and n is 0 then (R¹)_m is other than di-C₁₋₆alkyl,

15 di-halo or mono-halo-mono-C₁₋₆alkyl;

(iii) when R³ is hydrogen or methyl, m is 0, n is 1, R² is a substituent at the -2 position and X is-O- then Y cannot be methyl or benzyl; and

(iv) provided that when R³ is hydrogen, m is 0 and n is 3 then at least one R² must be other than methoxy (preferably at least two of the R² groups must be other than methoxy,

20 most preferably each R² must be other than methoxy).

Compounds of the invention may form salts which are within the ambit of the invention. Pharmaceutically acceptable salts are preferred although other salts may be useful in, for example, isolating or purifying compounds.

25 The term "aryl" refers to phenyl, naphthyl or a partially saturated bicyclic carbocyclic ring containing between 8 and 12 carbon atoms, preferably between 8 and 10 carbon atoms. Example of partially saturated bicyclic carbocyclic ring include: 1,2,3,4-tetrahydronaphthyl, indanyl, indenyl, 1,2,4a,5,8,8a-hexahydronaphthyl or 1,3a-dihydropentalene.

30 The term "halo" includes fluoro, chloro, bromo and iodo; preferably chloro, bromo and fluoro; most preferably fluoro.

The expression "-CH_{3-a}F_a" wherein a is an integer between 1 and 3 refers to a methyl group in which 1, 2 or all 3 hydrogen are replaced by a fluorine atom. Examples include: trifluoromethyl, difluoromethyl and fluoromethyl. An analogous notation is used with reference to the group -(CH₂)₁₋₄CH_{3-a}F_a, examples include: 2,2-difluoroethyl and

5 3,3,3-trifluoropropyl.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups. For example, "C₁₋₆alkyl" includes propyl, isopropyl and *t*-butyl.

The term "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH₂- group can optionally be replaced by a -C(O)- and sulphur atoms in a heterocyclic ring may be oxidised to S(O) or S(O)₂ groups. Preferably a "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring (preferably monocyclic of 5 or 6 atoms) containing 9 or 10 atoms of which 1 to 3 atoms are nitrogen, sulphur or oxygen,

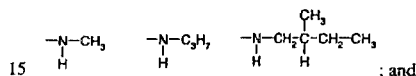
15 which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH₂- group can optionally be replaced by a -C(O)- or sulphur atoms in a heterocyclic ring may be oxidised to S(O) or S(O)₂ groups. Examples and suitable values of the term "heterocyclyl" are thiazolidinyl, pyrrolidinyl, pyrrolinyl, 2,5-dioxopyrrolidinyl, 2-benzoxazolinonyl, 1,1-dioxotetrahydrothienyl, 2,4-dioxoimidazolidinyl, 2-oxo-1,3,4-(4-triazolonyl), 20 2-oxazolidinonyl, 5,6-dihydrouracilyl, 1,3-benzodioxolyl, 1,2,4-oxadiazolyl, 2-azabicyclo[2.2.1]heptyl, 4-thiazolidonyl, morpholino, furanyl, 2-oxotetrahydrofuranlyl, tetrahydrofuranlyl, 2,3-dihydrobenzofuranlyl, benzothienyl, isoxazolyl, tetrahydropyranlyl, piperidyl, 1-oxo-1,3-dihydroisindolyl, piperazinyll, thiomorpholino, 1,1-dioxothiomorpholino, tetrahydropyranlyl, 1,3-dioxolanyl, homopiperazinyll, thienyl, 25 isoxazolyl, imidazolyl, pyrrolyl, thiazolyl, thiadiazolyl, isothiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, pyranlyl, indolyl, pyrimidyl, pyrazinyl, pyridazinyl, pyridyl, 4-pyridonyl, quinolyl, tetrahydrothienyl 1,1-dioxide, 2-oxo-pyrrolidinyl and 1-isoquinolonyl. Preferred examples of "heterocyclyl" when referring to a 5/6 and 6/6 bicyclic ring system include chromanlyl, benzofuranlyl, benzimidazolyl, benzthiophenyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, 30 benzisoxazolyl, pyridoimidazolyl, pyrimidoimidazolyl, quinolinyl, isoquinolinyl, quinoxalinyll, quinazolinyl, phthalazinyl, cinnolinyl, imidazo[2,1-b][1,3]thiazolyl and naphthyridinyl. Preferably the term "heterocyclyl" refers to 5- or 6-membered monocyclic

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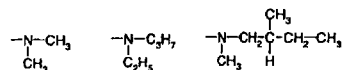
heterocyclic rings, such as oxazolyl, isoxazolyl, pyrrolidinyl, 2-pyrrolidonyl, 2,5-dioxopyrrolidinyl, morpholino, furanyl, tetrahydrofuranyl, piperidyl, piperazinyl, thiomorpholino, tetrahydropyranlyl, homopiperazinyl, thienyl, imidazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, indolyl, thiazolyl, thiadiazolyl, pyrazinyl, pyridazinyl and pyridyl.

- 5 The term "cycloalkyl" refers to a saturated carbocyclic ring containing between 3 to 12 carbon atoms, preferably between 3 and 7 carbon atoms. Examples of C₃₋₇-cycloalkyl include cycloheptyl, cyclohexyl, cyclopentyl, cyclobutyl or cyclopropyl. Preferably cyclopropyl, cyclopentyl or cyclohexyl.

- Examples of C₁₋₄alkyl include methyl, ethyl, propyl, isopropyl, 1-methyl-propyl, *sec*-butyl, *tert*-butyl and 2-ethyl-butyl; examples of C₂₋₆alkenyl include: ethenyl, 2-propenyl, 2-butenyl, or 2-methyl-2-butenyl; examples of C₂₋₆alkynyl include: ethynyl, 2-propynyl, 2-butylnyl, or 2-methyl-2-butylnyl, examples of -OC₁₋₄alkyl include methoxy, ethoxy, propoxy and *tert*-butoxy; examples of -C(O)OC₁₋₄alkyl include methoxycarbonyl, ethoxycarbonyl and *tert*-butoxycarbonyl; examples of -NH-C₁₋₄alkyl include:



examples of -N-di-(C₁₋₄alkyl):



For the avoidance of doubt, in the definition of linker group 'X', the right hand side of the group is attached to the phenyl ring and the left hand side is bound to 'Y'.

- 20 It is to be understood that, insofar as certain of the compounds of the invention may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of stimulating GLK directly or inhibiting the GLK/GLKRP interaction. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form.

Preferred compounds of Formula (I) to (Ic) above or of Formula (II) to (III) below are those wherein any one or more of the following apply:

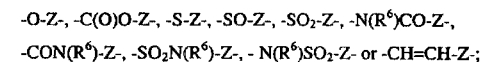
- (1) *m* is 0 or 1;

n is 1 or 2; preferably *n* is 2;

most preferably *m* is 0 and *n* is 2.

- (2) The R¹ and/or R² group(s) are attached at the 2-, 3- or 5- position relative to the carbonyl group; when *n* + *m* is 3, the groups are preferably at the 2-, 3- and 5- positions; when *n* + *m* is 2, the groups are preferably at the 3- and 5- positions; most preferably there are two groups in total, substituted at the 3- and 5- positions.
- (3) each R¹ is independently selected from OH, CH₃, F_a (preferably CF₃), halo, C₁₋₄alkyl (preferably methyl) and CN; preferably R¹ is selected from CH₃, F_a (preferably CF₃), halo, C₁₋₄alkyl (preferably methyl) and CN; most preferably R¹ is selected from -CH₃, F_a (preferably -CF₃), or halo.
- (4) each R² is the group Y-X-

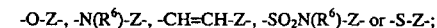
wherein each X is independently selected from:



- 15 preferably each X is selected from:



further preferably each X is selected from:



Most preferably each X is selected from:

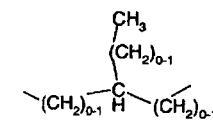
- 20 ---O---Z---, ---SO₂N(R⁶)---Z--- or ---N(R⁶)---Z---.

each Z is independently selected from:

a direct bond or -(CH₂)₁₋₂, or a group of the formula -(CH₂)_p-C(R⁶)₂-(CH₂)_q,

wherein one R⁶ group is hydrogen and the other R⁶ group is C₁₋₄alkyl;

preferably a direct bond, -(CH₂)₀₋₂ or



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more preferably a direct bond or -CH₂-.

each Z¹ is independently selected from:

a direct bond or -(CH₂)₁₋₂, or a group of the formula -(CH₂)_p-C(R⁶)₂-(CH₂)_q,

wherein one R⁶ group is hydrogen and the other R⁶ group is C₁₋₄alkyl;

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or

condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using

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one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

5 Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

10 For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

25 The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula (I), (Ia), (Ib) or (Ic) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula (I), (Ia), (Ib) or (Ic) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. 30 In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose

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in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

The elevation of GLK activity described herein may be applied as a sole therapy or may involve, in addition to the subject of the present invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example in the treatment of diabetes mellitus chemotherapy may include the following main categories of treatment:

- 10 1) Insulin and insulin analogues;
- 2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide) and prandial glucose regulators (for example repaglinide, nateglinide);
- 3) Insulin sensitising agents including PPAR γ agonists (for example pioglitazone and rosiglitazone);
- 15 4) Agents that suppress hepatic glucose output (for example metformin).
- 5) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);
- 6) Agents designed to treat the complications of prolonged hyperglycaemia;
- 7) Anti-obesity agents (for example sibutramine and orlistat);
- 20 8) Anti-dyslipidaemia agents such as, HMG-CoA reductase inhibitors (statins, eg pravastatin); PPAR α agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); bile acid absorption inhibitors (IBATi) and nicotinic acid and analogues (niacin and slow release formulations);
- 25 9) Antihypertensive agents such as, β blockers (eg atenolol, ideral); ACE inhibitors (eg lisinopril); Calcium antagonists (eg, nifedipine); Angiotensin receptor antagonists (eg candesartan); α antagonists and diuretic agents (eg, furosemide, benzthiazide);
- 10) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors);
- 30 antiplatelet agents (eg, aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin; and

X

- 90 -

No.	Route	2	3	5	MH+	M-H
90	3	H	(1-Methylpiperazin-4-yl)methoxy	Benzoyloxy	462	460
91	3	H	2-(N-morpholino)ethoxy	Benzoyloxy	478	
92	3	H	2-(Pyrid-4-yl)ethoxy	2-Methylbenzoyloxy	484	482
93	3	H	(4,6-Dimethoxypyrimid-2-yl)methoxy	2-Methylbenzoyloxy	531	529
94	3	H	Carboxymethoxy	2-Methylbenzoyloxy	437	435
95	4	H	Isopropoxy	2-(4-Methylthiazol-5-yl)ethoxy	442	440
96	4	H	Isopropoxy	2-Methylbenzoyloxy	421	419
97	4	H	Isopropoxy	(5-Methyl-isoxazol-3-yl)methoxy	412	410
98	4	H	Isopropoxy	Isobutoxy	373	371
99	5	H	2-Methylbenzoylamino	2-Methylbenzoylamino	509	
100	6	H	Phenoxymethyl	Phenoxymethyl	455	
101	5	H	Acetoxy	(2-Methyl)benzoyloxy	435	
102	5	H	H	(2-Chloro)benzoyloxy		
103	5	H	2-Difluoromethoxy-Benzoyloxy	2-Difluoromethoxy-Benzoyloxy	601	
104	5	H	2-Methylbenzoyloxy	2-Cyanobenzoyloxy	508	506
105	5	H	2-(N-morpholino)ethoxy	Benzoyloxy	492	

BIOLOGICALTests:

5 The biological effects of the compounds of the invention may be tested in the following way:

(1) Enzymatic activity of GLK may be measured by incubating GLK, ATP and glucose. The rate of product formation may be determined by coupling the assay to a G-6-P dehydrogenase, NADP/NADPH system and measuring the increase in optical density at 10 340nm (Matschinsky et al 1993).

(2) A GLK/GLKRP binding assay for measuring the binding interactions between GLK and GLKRP. The method may be used to identify compounds which modulate GLK by modulating the interaction between GLK and GLKRP. GLKRP and GLK are incubated with 15 an inhibitory concentration of F-6-P, optionally in the presence of test compound, and the extent of interaction between GLK and GLKRP is measured. Compounds which either

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displace F-6-P or in some other way reduce the GLK/GLKRP interaction will be detected by a decrease in the amount of GLK/GLKRP complex formed. Compounds which promote F-6-P binding or in some other way enhance the GLK/GLKRP interaction will be detected by an increase in the amount of GLK/GLKRP complex formed. A specific example of such a 5 binding assay is described below

GLK/GLKRP scintillation proximity assay

Recombinant human GLK and GLKRP were used to develop a "mix and measure" 96 well SPA (scintillation proximity assay). (A schematic representation of the assay is given in 10 Figure 3). GLK (Biotinylated) and GLKRP are incubated with streptavidin linked SPA beads (Amersham) in the presence of an inhibitory concentration of radiolabelled [3H]F-6-P (Amersham Custom Synthesis TRQ8689), giving a signal as depicted in Figure 3. Compounds which either displace the F-6-P or in some other way disrupt the GLK / GLKRP binding interaction will cause this signal to be lost.

15 Binding assays were performed at room temperature for 2 hours. The reaction mixtures contained 50mM Tris-HCl (pH = 7.5), 2mM ATP, 5mM MgCl₂, 0.5mM DTT, recombinant biotinylated GLK (0.1 mg), recombinant GLKRP (0.1 mg), 0.05mCi [3H] F-6-P (Amersham) to give a final volume of 100ml. Following incubation, the extent of GLK/GLKRP complex formation was determined by addition of 0.1mg/well avidin linked 20 SPA beads (Amersham) and scintillation counting on a Packard TopCount NXT.

The exemplified compounds described above were found to have an activity of at least 40% activity at 10 µm when tested in the GLK/GLKRP scintillation proximity assay.

25 (3) A F-6-P / GLKRP binding assay for measuring the binding interaction between GLKRP and F-6-P. This method may be used to provide further information on the mechanism of action of the compounds. Compounds identified in the GLK/GLKRP binding assay may modulate the interaction of GLK and GLKRP either by displacing F-6-P or by modifying the GLK/GLKRP interaction in some other way. For example, protein-protein 30 interactions are generally known to occur by interactions through multiple binding sites. It is thus possible that a compound which modifies the interaction between GLK and GLKRP could act by binding to one or more of several different binding sites.

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The F-6-P / GLKRP binding assay identifies only those compounds which modulate the interaction of GLK and GLKRP by displacing F-6-P from its binding site on GLKRP.

GLKRP is incubated with test compound and an inhibitory concentration of F-6-P, in the absence of GLK, and the extent of interaction between F-6-P and GLKRP is measured.

- 5 Compounds which displace the binding of F-6-P to GLKRP may be detected by a change in the amount of GLKRP/F-6-P complex formed. A specific example of such a binding assay is described below

F-6-P / GLKRP scintillation proximity assay

- 10 Recombinant human GLKRP was used to develop a "mix and measure" 96 well scintillation proximity assay. (A schematic representation of the assay is given in Figure 4). FLAG-tagged GLKRP is incubated with protein A coated SPA beads (Amersham) and an anti-FLAG antibody in the presence of an inhibitory concentration of radiolabelled [3H]F-6-P. A signal is generated as depicted in Figure 4. Compounds which displace the F-6-P will cause
15 this signal to be lost. A combination of this assay and the GLK/GLKRP binding assay will allow the observer to identify compounds which disrupt the GLK/GLKRP binding interaction by displacing F-6-P.

Binding assays were performed at room temperature for 2 hours. The reaction mixtures contained 50mM Tris-HCl (pH = 7.5), 2mM ATP, 5mM MgCl₂, 0.5mM DTT,

- 20 recombinant FLAG tagged GLKRP (0.1 mg), Anti-Flag M2 Antibody (0.2mg) (IBI Kodak), 0.05mCi [3H] F-6-P (Amersham) to give a final volume of 100ml. Following incubation, the extent of F-6-P/GLKRP complex formation was determined by addition of 0.1mg/well protein A linked SPA beads (Amersham) and scintillation counting on a Packard TopCount NXT.

25 Production of recombinant GLK and GLKRP:

Preparation of mRNA

Human liver total mRNA was prepared by polytron homogenisation in 4M guanidine isothiocyanate, 2.5mM citrate, 0.5% Sarkosyl, 100mM b-mercaptoethanol, followed by

- 30 centrifugation through 5.7M CsCl, 25mM sodium acetate at 135,000g (max) as described in Sambrook J, Fritsch EF & Maniatis T, 1989.

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Poly A⁺ mRNA was prepared directly using a FastTrack™ mRNA isolation kit (Invitrogen).

PCR amplification of GLK and GLKRP cDNA sequences

- 5 Human GLK and GLKRP cDNA was obtained by PCR from human hepatic mRNA using established techniques described in Sambrook, Fritsch & Maniatis, 1989. PCR primers were designed according to the GLK and GLKRP cDNA sequences shown in Tanizawa et al 1991 and Bonthron, D.T. et al 1994 (later corrected in Warner, J.P. 1995).

10 *Cloning in Bluescript II vectors*

GLK and GLKRP cDNA was cloned in E. coli using pBluescript II, (Short et al 1998) a recombinant cloning vector system similar to that employed by Yanisch-Perron C et al (1985), comprising a colEI-based replicon bearing a polylinker DNA fragment containing multiple unique restriction sites, flanked by bacteriophage T3 and T7 promoter sequences; a
15 filamentous phage origin of replication and an ampicillin drug resistance marker gene.

Transformations

- E. Coli transformations were generally carried out by electroporation. 400 ml cultures of strains DH5a or BL21(DE3) were grown in L-broth to an OD 600 of 0.5 and harvested by
20 centrifugation at 2,000g. The cells were washed twice in ice-cold deionised water, resuspended in 1ml 10% glycerol and stored in aliquots at -70°C. Ligation mixes were desalted using Millipore V series™ membranes (0.0025mm pore size). 40ml of cells were incubated with 1ml of ligation mix or plasmid DNA on ice for 10 minutes in 0.2cm electroporation cuvettes, and then pulsed using a Gene Pulser™ apparatus (BioRad) at
25 0.5kVcm⁻¹, 250mF, 250 ?. Transformants were selected on L-agar supplemented with tetracycline at 10mg/ml or ampicillin at 100mg/ml.

Expression

- GLK was expressed from the vector pTB375NBSE in E.coli BL21 cells, producing a
30 recombinant protein containing a 6-His tag immediately adjacent to the N-terminal methionine. Alternatively, another suitable vector is pET21(+)/DNA, Novagen, Cat number

KPE

697703. The 6-His tag was used to allow purification of the recombinant protein on a column packed with nickel-nitrilotriacetic acid agarose purchased from Qiagen (cat no 30250).

GLKRP was expressed from the vector pFLAG CTC (IBI Kodak) in E.coli BL21 cells, producing a recombinant protein containing a C-terminal FLAG tag. The protein was purified initially by DEAE Sepharose ion exchange followed by utilisation of the FLAG tag for final purification on an M2 anti-FLAG immunoaffinity column purchased from Sigma-Aldrich (cat no. A1205).

Biotinylation of GLK:

10 GLK was biotinylated by reaction with biotinamidocaproate N-hydroxysuccinimide ester (biotin-NHS) purchased from Sigma-Aldrich (cat no. B2643). Briefly, free amino groups of the target protein (GLK) are reacted with biotin-NHS at a defined molar ratio forming stable amide bonds resulting in a product containing covalently bound biotin. Excess, non-conjugated biotin-NHS is removed from the product by dialysis. Specifically, 7.5mg of GLK
15 was added to 0.31mg of biotin-NHS in 4mL of 25mM HEPES pH = 7.3, 0.15M KCl, 1mM dithiothreitol, 1mM EDTA, 1mM MgCl₂ (buffer A). This reaction mixture was dialysed against 100mL of buffer A containing a further 22mg of biotin-NHS. After 4hours excess biotin-NHS was removed by extensive dialysis against buffer A.

20 PHARMACEUTICAL COMPOSITIONS

The following illustrate representative pharmaceutical dosage forms of the invention as defined herein (the active ingredient being termed "Compound X"), for therapeutic or prophylactic use in humans:

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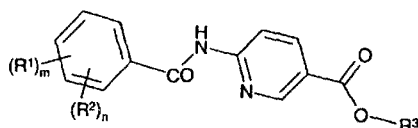
(a)	<u>Tablet I</u>	<u>mg/tablet</u>
	Compound X.....	100
	Lactose Ph.Eur.....	182.75
	Croscarmellose sodium.....	12.0
30	Maize starch paste (5% w/v paste).....	2.25
	Magnesium stearate.....	3.0

(b)	<u>Tablet II</u>	<u>mg/tablet</u>
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CLAIMS:

1. The use of a compound of Formula (I) or a salt, solvate or prodrug thereof, in the preparation of a medicament for use in the treatment or prevention of a disease or
- 5 medical condition mediated through GLK:



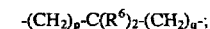
Formula (I)

wherein

- m is 0, 1 or 2;
- 10 n is 0, 1, 2, 3 or 4;
- and $n + m > 0$;
- each R^1 is independently selected from OH, $-(CH_2)_{1-4}OH$, $-CH_2F$, $-(CH_2)_{1-4}CH_2F$, halo, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, NO_2 , NH_2 , $-NH-C_{1-4}alkyl$, $-N-di-(C_{1-4}alkyl)$, CN or formyl;
- 15 each R^2 is the group Y-X-
- wherein each X is a linker independently selected from:
- $-O-Z-$, $-O-Z-O-Z-$, $-C(O)O-Z-$, $-OC(O)-Z-$, $-S-Z-$, $-SO-Z-$, $-SO_2-Z-$, $-N(R^6)-Z-$, $-N(R^6)SO_2-Z-$, $-SO_2N(R^6)-Z-$, $-(CH_2)_{1-4}-$, $-CH=CH-Z-$, $-C\equiv C-Z-$, $-N(R^6)CO-Z-$, $-CON(R^6)-Z-$, $-C(O)N(R^6)S(O)_2-Z-$, $-S(O)_2N(R^6)C(O)-Z-$, $-C(O)-Z-$ or a direct
- 20 bond;
- each Z is independently a direct bond or a group of the formula $-(CH_2)_p-C(R^6)_2-(CH_2)_q-$;
- each Y is independently selected from aryl- Z^1- , heterocyclyl- Z^1- , $C_{3-7}cycloalkyl-Z^1-$, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$ or $-(CH_2)_{1-4}CH_2F$;
- 25 wherein each Y is independently optionally substituted by up to 3 R^4 groups;
- each R^4 is independently selected from halo, $-CH_2F$, CN, NO_2 , NH_2 , $C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $-COOH$, $-C(O)OC_{1-6}alkyl$, OH or phenyl, or R^5-X^1 , where X^1 is independently as defined in X above and R^5 is selected from hydrogen, $C_{1-6}alkyl$, $-CH_2F$, phenyl, naphthyl,

heterocyclyl or $C_{3-7}cycloalkyl$; and R^5 is optionally substituted by halo, $C_{1-6}alkyl$, $-CH_2F$, CN, NO_2 , NH_2 , $COOH$ or $-C(O)OC_{1-6}alkyl$, wherein each phenyl, naphthyl or heterocyclyl ring in R^5 is optionally substituted by halo, CH_2F , CN, NO_2 , NH_2 , $C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $COOH$, $-C(O)OC_{1-6}alkyl$ or OH;

each Z^1 is independently a direct bond or a group of the formula



R^3 is selected from hydrogen or $C_{1-6}alkyl$; and

R^6 is independently selected from hydrogen, $C_{1-6}alkyl$ or $-C_{2-4}alkyl-O-C_{1-4}alkyl$;

10 each a is independently 1, 2 or 3;

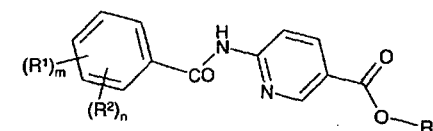
p is an integer between 0 and 2;

q is an integer between 0 and 2; and

$p + q < 4$.

- 15 2. A pharmaceutical composition comprising a compound of Formula (I) as claimed in claim 1, or a salt, solvate or prodrug thereof, together with a pharmaceutically-acceptable diluent or carrier for use in the preparation of a medicament for use in the treatment or prevention of a disease or medical condition mediated through GLK.

- 20 3. A compound of Formula (Ib) or a salt, solvate or prodrug thereof



Formula (Ib)

wherein

- m is 0, 1 or 2;
- 25 n is 0, 1, 2, 3 or 4;
- and $n + m > 0$;
- each R^1 is independently selected from OH, $-(CH_2)_{1-4}OH$, $-CH_2F$, $-(CH_2)_{1-4}CH_2F$, halo, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, NO_2 , NH_2 , $-NH-C_{1-4}alkyl$, $-N-di-(C_{1-4}alkyl)$, CN or formyl;

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

202075
Bogotá, D.C.,

Abogado
ALICIA LLOREDA RICAURTE.

ASUNTO	Radicación	05090931
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	6261
	Folios	015

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒

No. Sol. Internacional PCT/JP2004/001568
Fecha de Presentación Internal. 13 de Febrero de 2004.

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:

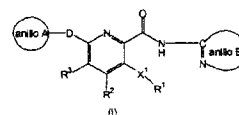
1. Documentos estudiados

- 1.1. Descripción: Folios: 99 a 403 (como se radicó inicialmente)
- 1.2. Reivindicaciones: Folios: 404 a 428 (como se radicó inicialmente)
- 1.3. Prioridad: Folio 1 (13-02-2003 , JP P2003-034987).
(01-10-2003 , JP P2003-342860).
(22-01-2004 , JP P2004-014799).

2. Objeto de la invención

Título de la solicitud: NOVEDOSOS DERIVADOS DE 2-PIRIDINCARBOXAMIDA.

El objeto de la presente solicitud de patente de invención consiste en:
Derivados de 2-piridincarboxamida.



Reivindicaciones 1- 34: Un Compuesto de fórmula I.

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Reivindicación 35 : Una composición farmacéutica que comprende un compuesto de fórmula I y otros activos.

Reivindicación 36 : Un activador de glucoquinasa que comprende un compuesto de fórmula I.

Reivindicaciones 37-38 : Un agente terapéutico que comprende un compuesto de fórmula I.

El problema planteado en esta solicitud es la necesidad de compuestos caracterizados por ser activadores de la glucoquinasa, útiles en el tratamiento para la diabetes y sus complicaciones y en el tratamiento de la obesidad.

Para solucionar este problema técnico la solicitud en estudio proporciona compuestos derivados de 2-piridincarboxamida, composiciones farmacéuticas y agentes terapéuticos que los contienen.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la Clasificación Internacional de Patentes (IPC): C07D401/14; A61K31/4439; A61K31/444; A61K31/497; A61K31/501; A61K31/506; A61K31/53; A61P3/04; A61P3/10; A61P9/00; A61P9/10; A61P13/12; A61P25/00; A61P27/02; A61P43/00; C07D413/14; C07D417/12; C07D417/14; C07D471/04; C07D513/04.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

- Las reivindicaciones 1,4,11,13-14, no son concisas ya que hay expresiones muy generales . Estas son :
 - Alquilo inferior, alcoxi inferior, alcanilo, alquilcarbamoilo inferior, hidroxialquilo, alquilcarbamoilo entre otros , ya que no se especifica el número de carbonos que los conforman .

Lo cual hace que no se pueda determinar que todos los compuestos obtenidos finalmente , presenten la actividad reclamada.

- La reivindicación 35 es muy amplia en el sentido que existen un número indefinido de composiciones obtenidas de combinar el compuesto de fórmula I con 1, 2 o más de los compuestos seleccionados de los numerales (a)-(g) . Se le requiere al interesado definir o especificar los compuestos que son relevantes para la composición reivindicada y que se encuentre debidamente sustentada en la descripción.
- En las reivindicaciones 37-38 se habla sobre un agente terapéutico y/o agente preventivo que comprende un compuesto I . Es necesario que el solicitante concrete de forma clara e inequívoca el objeto de la protección. Si es una forma farmacéutica o formulación farmacéutica en particular, las reivindicaciones también deben ser encabezadas acorde a tal decisión y caracterizada únicamente por los elementos técnicos que la conforman como principios activos, excipientes y proporciones.
- Para la composición farmacéutica de los compuestos de fórmula I con otros compuestos de los folios 427-428 (reivindicación 35) , esta Dependencia encuentra que dentro de la descripción se encuentran enunciadas dichas

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composiciones de los compuestos de fórmula I, con otras sustancias activas pero no se evidencia sustento técnico.

4. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 13 de Febrero de 2003, 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 :

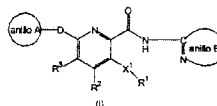
N°	Documento	Título	Fecha de Publicación*
D1	JP58121215	ANTIALLERGIC AGENT	19 de Julio de 1983
D2	WO03000267	AMINO NICOTINATE DERIVATIVES AS GLUCOKINASE (GLK) MODULATORS	3 de Enero de 2003

5. Análisis de patentabilidad (artículo 14 D486)

5.1. Novedad (artículo 16 D486)

Comparando elemento por elemento el objeto de esta solicitud con lo mencionado en las anterioridades, tenemos que:

La presente Solicitud de Patente Colombiana No. 05090931 se refiere a:

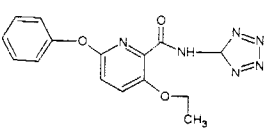
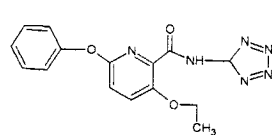


Compuestos de fórmula general (I)

Para las reivindicaciones 1,3-6,13.

D1 (Folios 26-49) enseña compuestos derivados de 2-piridincarboxamida, útiles como agentes antialérgicos.

SOLICITUD	D1
(I)	
En donde: Es un grupo arilo de 6-10 miembros. Es un grupo heteroarilo monocíclico. R² y R³ son hidrógeno. D es Oxígeno.	En donde : R² es un grupo fenoxi. R¹ es un grupo tioalquilo inferior.

 En donde:  Es un grupo arilo de 6-10 miembros.  Es un grupo heteroarilo monocíclico. R^2 y R^3 son hidrógeno. D es oxígeno. X^1 es O. y R^1 es un grupo alquilo inferior.	 En donde : R^2 es un grupo fenoxi. R^1 es un grupo alcoxi de bajo peso molecular.
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Estos compuestos específicos de la anterioridad D1 (Folios 26 y 27, reivindicación 1) son iguales a los compuestos de la presente solicitud.

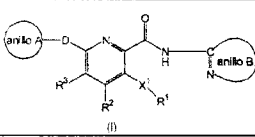
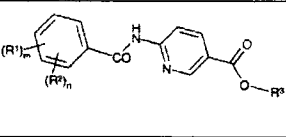
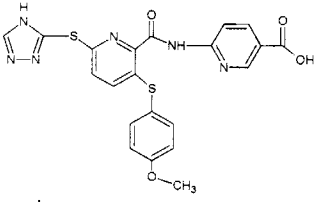
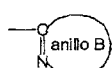
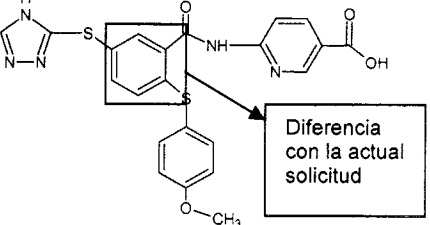
Como se observa, el elemento característico del compuesto reivindicado en 1,3-6,13 era conocido en D1 y está comprendido en el estado de la técnica, con lo cual se considera que NO cumple con el requisito de Novedad.

El activador de glucoquinasa de la reivindicación 36 y el agente terapéutico de las reivindicaciones (37 y 38) no son nuevos porque el compuesto que los caracteriza no es nuevo.

5.2. Nivel inventivo (artículo 18 D486)

Para las reivindicaciones 1-35.

Se realiza el siguiente cuadro comparativo:

SOLICITUD	D2
 (B)	
Según la reivindicación 1.  En donde .  El anillo A es un grupo heteroarilo de 5-7 miembros (triazolilo). R^3 y R^2 son hidrógeno. X^1 es S. R^1 es un grupo arilo de 6-10 miembros (fenilo) sustituido por un grupo alcoxi inferior.  El anillo B es un grupo heteroarilo monocíclico (piridil) sustituido por un grupo carboxilo.	Según la reivindicación 1.  En donde: m es 0. n es 2. R^3 es hidrógeno R^2 está ubicado en la 2 y 5 posición respecto al grupo carbonilo. R^2 en la segunda posición es un grupo Y-X- en donde: X es un grupo -S-Z- y Z es un enlace directo. Y es un grupo heterociclilo-Z¹-, y Z¹ es un enlace directo y heterociclilo es 1,2,4 triazolil. R^2 en la quinta posición es un grupo Y-X- en donde: X es un grupo -S-Z- y Z es un enlace directo. Y es un grupo arilo-Z¹-, y Z¹ es un enlace directo y arilo es fenilo sustituido por R^4 en donde R^4 es un grupo -OalquiloC₁₋₆ Diferencia con la actual solicitud

El documento del estado de la técnica más cercano es D2 (folios 484-492) que divulga compuestos caracterizados por ser moduladores de la glucoquinasa.

La diferencia con D2 es que en la actual solicitud el anillo central es un heteroarilo (piridina) mientras que en la anterioridad es un grupo arilo (fenilo) .

Esta diferencia no parece conceder un efecto técnico inesperado ò una ventaja a los compuestos reivindicados en comparación con los compuestos del Estado de la técnica más cercano, por que no parecen presentar un mayor efecto activador de la glucoquinasa .

Así que el Problema Técnico objetivo en esta solicitud que consiste en la necesidad de compuestos caracterizados por ser activadores de la glucoquinasa, útiles en el tratamiento para la diabetes y sus complicaciones y en el tratamiento de la obesidad, se había solucionado previamente mediante compuestos muy similares que no tienen el anillo heteroarilo (piridina) reivindicado en la actual solicitud . De manera que los nuevos compuestos son una alternativa a los compuestos conocidos porque no presentan un mayor efecto activador de la glucoquinasa .

El experto en la materia en vista del Estado de la Técnica en su totalidad, es decir en vista de D2 , hubiera sugerido sin mucho esfuerzo de su parte, modificar en D2 el anillo arilo (fenilo) por el anillo heteroarilo (piridina)divulgado en la actual solicitud (lo cual es una práctica común en el campo técnico) y así lograr los derivados de 2-piridincarboxamida reivindicados que no parecen presentar un mayor efecto activador de la glucoquinasa .

Por lo cual se consideran obvios para el experto en la materia. En consecuencia, carecen de nivel inventivo.

La composición farmacéutica de la reivindicación 35 carece de nivel inventivo a la luz de D2 (Ver folio 488, página 23, líneas 3-32), porque el compuesto de fórmula I que lo caracteriza no es inventivo.

6. Conclusión:

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

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	JP58121215	1,3-6,13,36-38.	Novedad.
D2	WO03000267	1- 38.	Nivel inventivo.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de 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.

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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.

[Handwritten signature]
ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

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

05 JUL 2011

CONCEPTO TÉCNICO No.
1251

EXAMINADOR TÉCNICO
Código No. 202075