

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-054873- -00003-0001

Fecha: 2007-09-21 09:44:13 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 344 DESGLOSE
Act. 411 PRESENTACION Folios: 1

jllore@lloredacarrasco.com

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: P1.-F. HOFFMANN LA ROCHE AG.- Patente de Invención en Fase
Nacional PCT para "ACTIVADORES DE GLUCOQUINASA PIRIDIN O
PIRAZIN-5-SUSTITUIDOS".- Clase C07D 241/46.-Expediente número 05-
054.873.-

1. Me refiero a mi memorial de 19 de Septiembre de 2007.
2. Por medio del presente escrito, atentamente me permito solicitar a ese despacho, el desglose del recibo de pago allegado con mi memorial arriba mencionado, ya que por un error involuntario se presentó, siendo que este trámite solamente aplica para las solicitudes PCT Sin Publicar, según la respuesta emitida por ese Despacho al Derecho de Petición cuyo número es: 07-089.021.
3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad a la mayor brevedad posible.

Señor Superintendente,


ALICIA LLOREDA RICAURTE
T.P. 53.215

2020
Bogotá, D.C.,

Doctora:
Alicia Lloreda Ricaurte
Apoderada

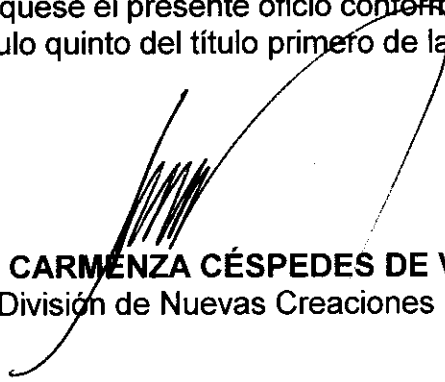
Oficio N°: 4994

ASUNTO:	Radicación PCT N°	05-54873
	Trámite	011
	Evento	344
	Actuación	330
	Folios	002

Atendiendo la solicitud contenida en el escrito de fecha 21 de septiembre del 2007 radicado bajo el número 05-054873-00003-0001, ordenase el desglose del recibo de caja N° 74,056 por valor de noventa y nueve mil pesos mcte (\$99.000.00) el cual obra a folio 451 del expediente administrativo, dejando copia dentro del mismo, previa entrega del original al solicitante para su aplicación a otro trámite ante esta Superintendencia.

Envíese copia del presente oficio a la División Financiera, para lo de su competencia.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.



ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe División de Nuevas Creaciones

El anterior oficio fue notificado por fijación en lista de fecha, _____.

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 05-54873

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **556** DE

FECHA **30** DE **SEPTIEMBRE DE 2005** EL TERMINO HABIL SEÑALADO POR

LA LEY EXPIRA EL **29** DE **DICIEMBRE DEL 2005**

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 ☒



US 20020002190A1

(19) **United States**

(12) **Patent Application Publication**

Corbett et al.

(10) **Pub. No.: US 2002/0002190 A1**

(43) **Pub. Date: Jan. 3, 2002**

(54) **PARA-ARYL OR HETEROCYCLIC
SUBSTITUTED PHENYL GLUCOKINASE
ACTIVATORS**

(76) **Inventors: Wendy L. Corbett, Randolph, NJ (US);
Nancy-Ellen Haynes, Cranford, NJ
(US); Ramakanth Sarabu, Pine Brook,
NJ (US)**

**Correspondence Address:
HOFFMANN-LA ROCHE INC.
PATENT LAW DEPARTMENT
340 KINGSLAND STREET
NUTLEY, NJ 07110**

(21) **Appl. No.: 09/846,821**

(22) **Filed: May 1, 2001**

Related U.S. Application Data

(63) **Non-provisional of provisional application No.
60/202,387, filed on May 8, 2000.**

Publication Classification

(51) **Int. Cl.⁷ A61K 31/4439; A61K 31/426;
A61K 31/427; C07D 417/02;
C07D 277/18**
(52) **U.S. Cl. 514/349; 514/370; 548/192;
546/270.4**

(57) **ABSTRACT**

Para-aryl or heteroaryl substituted phenyl amides which are active as glucokinase activators to increase insulin secretion which makes them useful for treating type II diabetes.

PARA-ARYL OR HETEROCYCLIC SUBSTITUTED PHENYL GLUCOKINASE ACTIVATORS

PRIORITY TO PROVISIONAL APPLICATION(S)
UNDER 35 U.S.C. § 119(e)

[0001] This application claims priority under 35 U.S.C. §119(e) of provisional application Ser. No. 60/202,387, filed on May 8, 2000.

BACKGROUND OF THE INVENTION

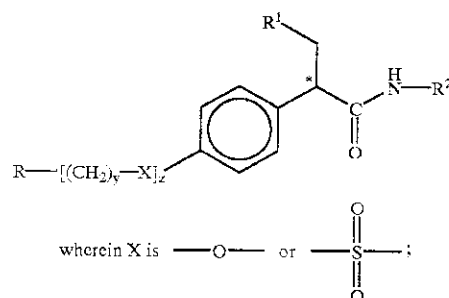
[0002] Glucokinase (GK) is one of four hexokinases found in mammals [Colowick, S. P., in *The Enzymes*, Vol. 9 (P. Boyer, ed.) Academic Press, New York, N.Y., pages 1-48, 1973]. The hexokinases catalyze the first step in the metabolism of glucose, i.e., the conversion of glucose to glucose-6-phosphate. Glucokinase has a limited cellular distribution, being found principally in pancreatic β -cells and liver parenchymal cells. In addition, GK is a rate-controlling enzyme for glucose metabolism in these two cell types that are known to play critical roles in whole-body glucose homeostasis [Chipkin, S. R., Kelly, K. L., and Ruderman, N. B. in *Jostlin's Diabetes* (C. R. Khan and G. C. Wier, eds.), Lea and Febiger, Philadelphia, Pa., pages 97-115, 1994]. The concentration of glucose at which GK demonstrates half-maximal activity is approximately 8 mM. The other three hexokinases are saturated with glucose at much lower concentrations (<1 mM). Therefore, the flux of glucose through the GK pathway rises as the concentration of glucose in the blood increases from fasting (5 mM) to postprandial (>10-15 mM) levels following a carbohydrate-containing meal [Printz, R. G., Magnuson, M. A., and Granner, D. K. in *Ann. Rev. Nutrition Vol. 13* (R. E. Olson, D. M. Bier, and D. B. McCormick, eds.), Annual Review, Inc., Palo Alto, Calif., pages 463-496, 1993]. These findings contributed over a decade ago to the hypothesis that GK functions as a glucose sensor in β -cells and hepatocytes (Meglasson, M. D. and Matschinsky, F. M. *Amer. J. Physiol.* 246, E1-E13, 1984). In recent years, studies in transgenic animals have confirmed that GK does indeed play a critical role in whole-body glucose homeostasis. Animals that do not express GK die within days of birth with severe diabetes while animals overexpressing GK have improved glucose tolerance (Grupe, A., Hultgren, B., Ryan, A. et al., *Cell* 83, 69-78, 1995; Ferrie, T., Riu, E., Bosch, F. et al., *FASEB J.*, 10, 1213-1218, 1996). An increase in glucose exposure is coupled through GK in β -cells to increased insulin secretion and in hepatocytes to increased glycogen deposition and perhaps decreased glucose production.

[0003] The finding that type II maturity-onset diabetes of the young (MODY-2) is caused by loss of function mutations in the GK gene suggests that GK also functions as a glucose sensor in humans (Liang, Y., Kesavan, P., Wang, L. et al., *Biochem. J.* 309, 167-173, 1995). Additional evidence supporting an important role for GK in the regulation of glucose metabolism in humans was provided by the identification of patients that express a mutant form of GK with increased enzymatic activity. These patients exhibit a fasting hypoglycemia associated with an inappropriately elevated level of plasma insulin (Glaser, B., Kesavan, P., Heyman, M. et al., *New England J. Med.* 338, 226-230, 1998). While mutations of the GK gene are not found in the majority of patients with type II diabetes, compounds that activate GK and, thereby, increase the sensitivity of the GK sensor

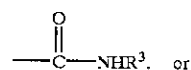
system will still be useful in the treatment of the hyperglycemia characteristic of all type II diabetes. Glucokinase activators will increase the flux of glucose metabolism in β -cells and hepatocytes, which will be coupled to increased insulin secretion. Such agents would be useful for treating type II diabetes.

SUMMARY OF THE INVENTION

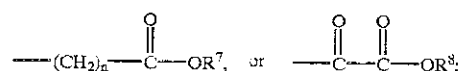
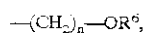
[0004] This invention provides a compound, comprising an amide of the formula:



[0005] R is a heteroaromatic ring, connected by a ring carbon atom, which contains from 5 to 6 ring members with from 1 to 3 heteroatoms selected from the group consisting of oxygen, sulfur or nitrogen, aryl containing 6 or 10 ring carbon atoms, aryl fused with a heteroaromatic ring which contains from 5 to 6 ring members with 1 to 3 heteroatoms in the ring being selected from the group consisting of nitrogen, oxygen or sulfur, a saturated 5- or 6-membered cycloheteroalkyl ring which contains from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, or a cycloalkyl ring having 5 or 6 carbon atoms; R¹ is a cycloalkyl ring having from 5 or 6 carbon atoms; R² is



[0006] a five- or six-membered heteroaromatic ring connected by a ring carbon atom to the amide group shown, which contains from 1 to 3 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen with a first heteroatom being nitrogen adjacent to the connecting ring carbon atom, said heteroaromatic ring being unsubstituted or monosubstituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl,



[0007] n is 0, 1, 2, 3 or 4; y and z are independently 0 or 1; R³ is hydrogen, lower alkyl or

celite was washed with ethyl acetate. The filtrate was concentrated in vacuo. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 1-[3-cyclopentyl-2-(3,4-difluoro-phenyl)-propionyl]-3-methyl-urea (12.6 mg, 18.7%) as a white solid: mp 244-246° C.; FAB-HRMS m/e calcd for $C_{16}H_{20}F_2N_2O_2$ (M+H)⁺ 421.2153, found 421.2161.

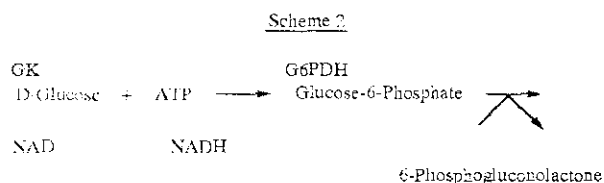
BIOLOGICAL ACTIVITY EXAMPLES

EXAMPLE A

In Vitro Glucokinase Activity

[0264] Glucokinase Assay:

[0265] Glucokinase (GK) was assayed by coupling the production of glucose-6-phosphate to the generation of NADH with glucose-6-phosphate dehydrogenase (G6PDH, 0.75-1 kunits/mg; Boehringer Mannheim, Indianapolis, IN) from *Leuconostoc mesenteroides* as the coupling enzyme (Scheme 2). Recombinant



[0266] Human liver GK1 was expressed in *E. coli* as a glutathione S-transferase fusion protein (GST-GK) [Liang et al, 1995] and was purified by chromatography over a glutathione-Sepharose 4B affinity column using the procedure provided by the manufacturer (Amersham Pharmacia Biotech, Piscataway, N.J.). Previous studies have demonstrated that the enzymatic properties of native GK and GST-GK are essentially identical (Liang et al, 1995; Neet et al., 1990).

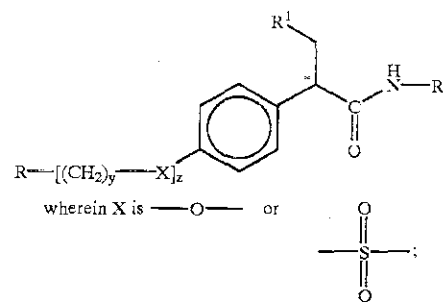
[0267] The assay was conducted at 25° C. in a flat bottom 96-well tissue culture plate from Costar (Cambridge, Mass.) with a final incubation volume of 120 μ l. The incubation mixture contained: 25 mM Hepes buffer (pH, 7.1), 25 mM KCl, 5 mM D-glucose, 1 mM ATP, 1.8 mM NAD, 2 mM $MgCl_2$, 1 μ M sorbitol-6-phosphate, 1 mM dithiothreitol, test drug or 10% DMSO, 1.8 unit/ml G6PDH, and GK (see below). All organic reagents were >98% pure and were from Boehringer Mannheim with the exceptions of D-glucose and Hepes that were from Sigma Chemical Co, St Louis, Mo. Test compounds were dissolved in DMSO and were added to the incubation mixture minus GST-GK in a volume of 12 μ l to yield a final DMSO concentration of 10%. This mix was preincubated in the temperature controlled chamber of a SPECTRAMax 250 microplate spectrophotometer (Molecular Devices Corporation, Sunnyvale, Calif.) for 10 minutes to allow temperature equilibrium and then the reaction was started by the addition of 20 μ l GST-GK.

[0268] After addition of enzyme, the increase in optical density (OD) at 340 nm was monitored over a 10 minute incubation period as a measure of GK activity. Sufficient GST-GK was added to produce an increase in OD₃₄₀ of 0.08 to 0.1 units over the 10 minute incubation period in wells

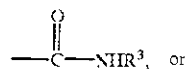
containing 10% DMSO, but no test compound. Preliminary experiments established that the GK reaction was linear over this period of time even in the presence of activators that produced a 5-fold increase in GK activity. The GK activity in control wells was compared with the activity in wells containing test GK activators, and the concentration of activator that produced a 50% increase in the activity of GK, i.e., the SC_{1.5}, was calculated. All of the compounds of formula I described in the Synthesis Examples had an SC_{1.5} less than or equal to 30 μ M.

What is claimed is:

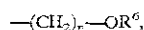
1. An amide selected from the group consisting of a compound of the formula



wherein R is a heteroaromatic ring, connected by a ring carbon atom, which contains from 5 to 6 ring members with from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur or nitrogen, aryl containing 6 or 10 ring carbon atoms, aryl containing from 6 to 10 ring carbon atoms fused with a heteroaromatic ring containing 5 or 6 ring members with 1 or 2 heteroatoms in the ring being selected from the group consisting of nitrogen, oxygen or sulfur, or a saturated 5- or 6-membered cycloheteroalkyl ring, which contains from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, or a cycloalkyl ring having 5 or 6 carbon atoms; R¹ is a cycloalkyl ring having 5 or 6 carbon atoms; R² is



a five- or six-membered heteroaromatic ring connected by a ring carbon atom to the amide group shown, which heteroaromatic ring contains from 1 to 3 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen with a first heteroatom being nitrogen which is adjacent to the connecting ring carbon atom, said heteroaromatic ring being unsubstituted or monosubstituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl,





US 20020042512A1

(19) **United States**

(12) **Patent Application Publication**

Kester et al.

(10) **Pub. No.: US 2002/0042512 A1**

(43) **Pub. Date: Apr. 11, 2002**

(54) **ALPHA-ACYL- AND
ALPHA-HETEROATOM-SUBSTITUTED
BENZENE ACETAMIDE GLUCOKINASE
ACTIVATORS**

(76) **Inventors: Robert F. Kester, West Orange, NJ
(US); Ramakanth Sarabu, Pine Brook,
NJ (US)**

**Correspondence Address:
HOFFMANN-LA ROCHE INC.
PATENT LAW DEPARTMENT
340 KINGSLAND STREET
NUTLEY, NJ 07110**

(21) **Appl. No.: 09/905,152**

(22) **Filed: Jul. 13, 2001**

Related U.S. Application Data

(63) **Non-provisional of provisional application No.
60/219,872, filed on Jul. 20, 2000.**

Publication Classification

(51) **Int. Cl.⁷ C07D 241/18; C07D 239/34;
C07D 237/14; C07D 213/72**
(52) **U.S. Cl. 544/239; 544/298; 544/336;
546/291; 564/165**

(57) **ABSTRACT**

**Substituted benzene acetamide compounds which are glu-
cokinase activators and pharmaceutically acceptable salts
thereof.**

ALPHA-ACYL- AND ALPHA-HETEROATOM-SUBSTITUTED BENZENE ACETAMIDE GLUCOKINASE ACTIVATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is related to U.S. Provisional Ser. No. 60/219,872, filed Jul. 20, 2000.

BACKGROUND OF THE INVENTION

[0002] This application is relevant to U.S. Ser. No. 09/526,143, filed Mar. 15, 2000, and U.S. Ser. No. 09/532,506, filed Mar. 21, 2000.

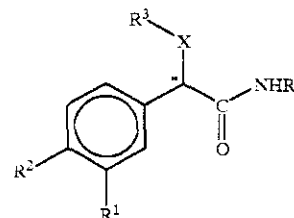
[0003] Glucokinase (GK) is one of four hexokinases found in mammals [Colowick, S. P., in *The Enzymes*, Vol. 9 (P. Boyer, ed.) Academic Press, New York, N.Y., pages 1-48, 1973]. The hexokinases catalyze the first step in the metabolism of glucose, i.e., the conversion of glucose to glucose-6-phosphate. Glucokinase has a limited cellular distribution, being found principally in pancreatic β -cells and liver parenchymal cells. In addition, GK is a rate-controlling enzyme for glucose metabolism in these two cell types that are known to play critical roles in whole-body glucose homeostasis [Chipkin, S. R., Kelly, K. L., and Ruderman, N. B. in *Joslin's Diabetes* (C. R. Khan and G. C. Wier, eds.), Lea and Febiger, Philadelphia, Pa., pages 97-115, 1994]. The concentration of glucose at which GK demonstrates half-maximal activity is approximately 8 mM. The other three hexokinases are saturated with glucose at much lower concentrations (<1 mM). Therefore, the flux of glucose through the GK pathway rises as the concentration of glucose in the blood increases from fasting (5 mM) to postprandial ($\approx$ 10-15 mM) levels following a carbohydrate-containing meal [Printz, R. G., Magnuson, M. A., and Granner, D. K. in *Ann. Rev. Nutrition* Vol. 13 (R. E. Olson, D. M. Bier, and D. B. McCormick, eds.), Annual Review, Inc., Palo Alto, Calif., pages 463-496, 1993]. These findings contributed over a decade ago to the hypothesis that GK functions as a glucose sensor in β -cells and hepatocytes (Meglasson, M. D. and Matschinsky, F. M. *Amer. J. Physiol.* 246, E1-E13, 1984). In recent years, studies in transgenic animals have confirmed that GK does indeed play a critical role in whole-body glucose homeostasis. Animals that do not express GK die within days of birth with severe diabetes while animals overexpressing GK have improved glucose tolerance (Grupe, A., Hultgren, B., Ryan, A. et al., *Cell* 83, 69-78, 1995; Ferric, T., Riu, E., Bosch, F. et al., *FASEB J.* 10, 1213-1218, 1996). An increase in glucose exposure is coupled through GK in β -cells to increased insulin secretion and in hepatocytes to increased glycogen deposition and perhaps decreased glucose production.

[0004] The finding that type II maturity-onset diabetes of the young (MODY-2) is caused by loss of function mutations in the GK gene suggests that GK also functions as a glucose sensor in humans (Liang, Y., Kesavan, P., Wang, L. et al., *Biochem. J.* 309, 167-173, 1995). Additional evidence supporting an important role for GK in the regulation of glucose metabolism in humans was provided by the identification of patients that express a mutant form of GK with increased enzymatic activity. These patients exhibit a fasting hypoglycemia associated with an inappropriately elevated level of plasma insulin (Glaser, B., Kesavan, P., Heyman, M.

et al., *New England J. Med.* 338, 226-230, 1998). While mutations of the GK gene are not found in the majority of patients with type II diabetes, compounds that activate GK and, thereby, increase the sensitivity of the GK sensor system will still be useful in the treatment of the hyperglycemia characteristic of all type II diabetes. Glucokinase activators will increase the flux of glucose metabolism in β -cells and hepatocytes, which will be coupled to increased insulin secretion. Such agents would be useful for treating type II diabetes.

SUMMARY OF THE INVENTION

[0005] This invention provides an amide selected from the group consisting of a compound of the formula:



[0006] wherein R¹ and R² are independently hydrogen, halo, cyano, nitro, lower alkylthio, perfluoro lower alkylthio, lower alkyl sulfonyl, or perfluoro-lower alkyl sulfonyl, R³ is lower alkyl having from 2 to 4 carbon atoms or a 5 to 7-membered ring which is cycloalkyl, cycloalkenyl, or heterocycloalkyl having one heteroatom selected from oxygen and sulfur, R⁴ is -C(O)NHR⁵, or is R⁶, which is an unsubstituted or mono-substituted five- or six-membered heteroaromatic ring connected by a ring carbon atom to the amide group shown, which five- or six-membered heteroaromatic ring contains from 1 to 3 heteroatoms selected from sulfur, oxygen or nitrogen, with one heteroatom being nitrogen which is adjacent to the connecting ring carbon atom; with said mono-substituted heteroaromatic ring being monosubstituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl, halo, nitro, cyano, -(CH₂)_n-OR⁹, -(CH₂)_n-C(O)-OR¹⁰, -(CH₂)_n-C(O)-NH-R¹¹, -C(O)-C(O)-OR¹², -(CH₂)_n-NHR¹³; n is 0, 1, 2, 3 or 4; R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³ are independently hydrogen or lower alkyl, R⁵ is hydrogen, lower alkyl, lower alkenyl, hydroxy lower alkyl, halo lower alkyl, -(CH₂)_n-C(O)-OR⁷, -C(O)-(CH₂)_n-C(O)-OR⁸, X is oxygen, sulfur, sulfonyl, or carbonyl; the * indicates an asymmetric carbon atom; and its pharmaceutically acceptable salts.

[0007] Preferably, the compound of formula I is in the "R" configuration at the asymmetric carbon, shown except in the case where X is carbonyl (C=O), when the preferred enantiomer is "S".

[0008] The compounds of formula I have been found to activate glucokinase. Glucokinase activators are useful in the treatment of type II diabetes.

[0167] To a solution of (3,4-dichloro-phenyl)-acetic acid (500 mg, 2.4 mmol) in *N,N*-dimethylformamide (15 mL) at 25° C. was added IIBTU (1.02 g, 2.7 mmol), 2-aminothiazole (360 mg, 3.6 mmol) and diisopropylethylamine (1.25 mL, 7.2 mmol). The reaction mixture was stirred for 16 h, then was diluted with water (10 mL) and extracted with ethyl acetate (3×15 mL). The combined organic layers were washed in turn with water (1×10 mL), 1N sodium hydroxide (1×10 mL), 1 N hydrochloric acid (1×10 mL) and brine (1×10 mL), then were dried over sodium sulfate, filtered and evaporated under reduced pressure. The residual material was purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) to furnish rac-2-(3,4-dichloro-phenyl)-*N*-thiazol-2-yl-acetamide (480 mg, 70% yield) as a light yellow solid, mp 169.8- 172.3° C. EI-HRMS *m/e* calcd for $C_{11}H_8N_2O_2SCl_2$ (M^+) 285.9734, found 285.9734.

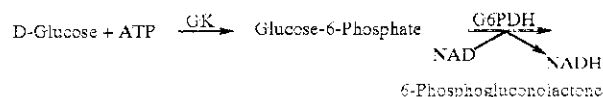
[0168] To a solution of rac-2-(3,4-dichloro-phenyl)-*N*-thiazol-2-yl-acetamide (185 mg, 0.64 mmol) in tetrahydrofuran (15 mL), previously cooled to -78° C., was added slowly a 1.0 M solution of lithium bis(trimethylsilyl)amide (1.3 mL, 1.3 mmol). The solution was stirred for 15 min at -78° C., then cyclopentanecarbonyl chloride (0.08 mL, 0.64 mmol) was dropwise added. The reaction mixture was stirred for an additional 60 min at -78° C. before it was quenched by the addition of a saturated ammonium chloride solution (10 mL). The mixture was then extracted with ethyl acetate (3×10 mL), dried over sodium sulfate, filtered and concentrated in vacuo. The product was purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) to afford 3-cyclopentyl-2-(3,4-dichloro-phenyl)-3-oxo-*N*-thiazol-2-yl-propionamide (98 mg, 40% yield) as a yellow-orange solid: EI-HRMS *m/e* calcd for $C_{17}H_{16}N_2O_2SCl_2$ (M^+) 382.0309, found 382.0309.

Biological Activity Example

[0169] a) In Vitro Glucokinase Activity

[0170] Glucokinase Assay: Glucokinase (GK) was assayed by coupling the production of glucose-6-phosphate to the generation of NADH with glucose-6-phosphate dehydrogenase (G6PDH, 0.75-1 kunits/mg; Boehringer Mannheim, Indianapolis, Ind.) from *Leuconostoc mesenteroides* as the coupling enzyme (Scheme 2). Recombinant

Scheme 2



[0171] Human liver GK1 was expressed in *E. coli* as a glutathione S-transferase fusion protein (GST-GK) [Liang et al, 1995] and was purified by chromatography over a glutathione-Sepharose 4B affinity column using the procedure provided by the manufacturer (Amersham Pharmacia Biotech, Piscataway, N.J.). Previous studies have demonstrated that the enzymatic properties of native GK and GST-GK are essentially identical (Liang et al, 1995; Neet et al., 1990).

[0172] The assay was conducted at 25° C. in a flat bottom 96-well tissue culture plate from Costar (Cambridge, Mass.)

with a final incubation volume of 120 μ L. The incubation mixture contained: 25 mM Hepes buffer (pH, 7.1), 25 mM KCl, 5 mM D-glucose, 1 mM ATP, 1.8 mM NAD, 2 mM $MgCl_2$, 1 μ M sorbitol-6-phosphate, 1 mM dithiothreitol, test drug or 10% DMSO, 1.8 unit/ml G6PDH, and GK (see below). All organic reagents were >98 % pure and were from Boehringer Mannheim with the exceptions of D-glucose and Hepes that were from Sigma Chemical Co, St Louis, Mo. Test compounds were dissolved in DMSO and were added to the incubation mixture minus GST-GK in a volume of 12 μ L to yield a final DMSO concentration of 10%. This mix was preincubated in the temperature controlled chamber of a SPECTRAMax 250 microplate spectrophotometer (Molecular Devices Corporation, Sunnyvale, Calif.) for 10 minutes to allow temperature equilibrium and then the reaction was started by the addition of 20 μ L GST-GK.

[0173] After addition of enzyme, the increase in optical density (OD) at 340 nm was monitored over a 10 minute incubation period as a measure of GK activity. Sufficient GST-GK was added to produce an increase in OD_{340} of 0.08 to 0.1 units over the 10 minute incubation period in wells containing 10% DMSO, but no test compound. Preliminary experiments established that the GK reaction was linear over this period of time even in the presence of activators that produced a 5-fold increase in GK activity. The GK activity in control wells was compared with the activity in wells containing test GK activators, and the concentration of activator that produced a 50% increase in the activity of GK, i.e., the $SC_{1.5}$, was calculated. All of the compounds of formula I described in the Synthesis Examples had an $SC_{1.5}$ less than or equal to 30 μ M.

[0174] Liang, Y., Kesavan, P., Wang, L., Niswender, K., Tanizawa, Y., Permut, M. A., Magnuson, M., and Matschinsky, F. M. Variable effects of maturity-onset-diabetes-of-youth (MODY)-associated glucokinase mutations on the substrate interactions and stability of the enzyme. *Biochem. J* 309: 167-173, 1995.

[0175] Neet, K., Keenan, R. P., and Tippet, P.S. Observation of a kinetic slow transition in monomeric glucokinase. *Biochemistry* 29:770-777, 1990.

[0176] b) In Vivo Activity

[0177] Glucokinase Activator in vivo Screen Protocol

[0178] C57BL/6J mice are orally dosed via gavage with Glucokinase (GK) activator at 50 mg/kg body weight following a two hour fasting period. Blood glucose determinations are made five times during the six hour post-dose study period.

[0179] Mice (n=6) are weighed and fasted for a two hour period prior to oral treatment. GK activators are formulated at 6.76 mg/ml in Gelucire vehicle (Ethanol:Gelucire44/14:PEG400q.s. 4:66:30 v/w/v). Mice are dosed orally with 7.5 μ L formulation per gram of body weight to equal a 50 mg/kg dose. Immediately prior to dosing, a pre dose (time zero) blood glucose reading is acquired by snipping off a small portion of the animals tail (~1 mm) and collecting 15 μ L blood into a heparinized capillary tube for analysis. Following GK activator administration, additional blood glucose readings are taken at 1, 2, 4, and 6 hours post dose from the same tail wound. Results are interpreted by comparing the mean blood glucose values of six vehicle treated mice with six GK activator treated mice over the six hour

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

2020
Bogotá, D.C

Abogado
ALICIA LLOREDA RICAURTE

ASUNTO	Radicación	05-54873
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	0706
	Folios	11

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

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

No. Sol. Internacional PCT/EP2003/014055
Fecha de Presentación Internal. 11-12-2003

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

1. Documentos estudiados

Descripción: Folios: 80 a 375 (como se radicó inicialmente)

Reivindicaciones: Folios 376 a 400 (como se radicó inicialmente)
Folios 452 a 476 (modificación).

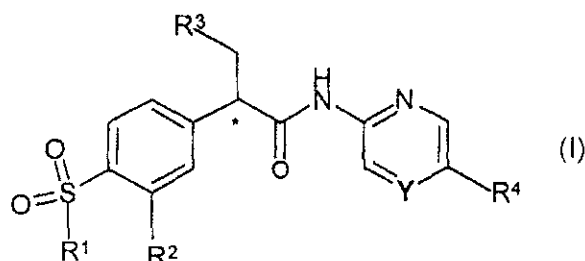
Prioridad: Folio: 1
Fecha: 12-12-2002; país y número: US60/432,806.
Fecha: 24-11-2003; país y número: US60/524,531.

2. Objeto de la Invención

Título de la invención: "ACTIVADORES DE GLUCOQUINASA PIRIDIN O PIRAZIN-5-SUSTITUIDOS"

Problema Técnico Planteado: La necesidad de agentes que activen la

Solución: Compuestos derivados de la fórmula (I):



IPC: A61P3/10; C07D213/75; A61K31/50.

3. De la solicitud de Patente

a. Reivindicaciones (artículo 30 D 486)

La reivindicación 1 carece de concisión debido a el amplio numero de sustituyentes posibles para R⁴, los cuales presentan marcadas diferencias estructurales entre si. No es posible a partir de la información contenida en la descripción establecer si todos los compuestos poseen la actividad terapéutica que el solicitante les atribuye debido al limitado número de compuestos ensayados. El solicitante debe limitar su reclamación a aquella materia sobre la que posea soporte suficiente en la descripción que permita establecer que realmente son una solución al problema técnico planteado.

La reivindicación 72 caracteriza un compuesto por su uso. Este tipo de caracterización no es admitida ya que el uso no es una característica técnica de un producto.

La reivindicación 74 caracteriza un compuesto por su método de preparación. Un producto definido en términos de un proceso de preparación es admisible solo si el producto no se puede definir por sus características estructurales, lo cual no corresponde al presente caso ya que los compuestos que aquí se reclaman si pueden definirse estructuralmente. En consecuencia la forma como se caracteriza esta reivindicación no es aceptada.

Por lo anterior, las reivindicaciones mencionadas no cumplen con el requisito de definición, concisión y sustento por la descripción de acuerdo al art. 30 de la Decisión 486.y/o art.22 Tratado PCT.

4. 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 12-12-2002

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
D1	US2002/0002190	PARA-ARYL OR HETEROCYCLIC SUBSTITUTED PHENYL GLUCOKINASE ACTIVATORS	3-01-2002
D2	US2002/0042512	ALPHA-ACYL-AND ALPHA-HETEROATOM-SUBSTITUTED BENZENE ACETAMIDE GLUCOKINASE ACTIVATORS	11-04-2002

5. Análisis de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

1) Respecto a la solicitud en estudio:

La reivindicación 1 reclama compuestos de la fórmula (I).

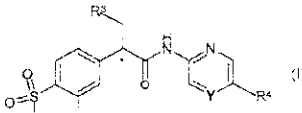
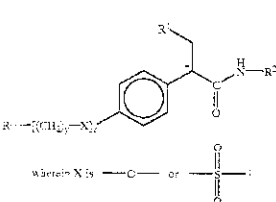
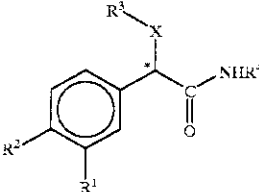
La reivindicación 68 reclama una composición farmacéutica que comprende un compuesto de fórmula (I).

2) Respecto al estado de la Técnica:

D1 divulga activadores de la glucoquinasa, del tipo fenil sustituidos con un anillo heterocíclico.

D2 divulga activadores de glucoquinasa, cuya estructura fundamental es heteroaril benceno acetamida.

3) Análisis de las diferencias con respecto al estado de la técnica:

Características esenciales de la Solicitud	D1	D2
	US2002/0002190	US2002/0042512
 (I)	 wherein X is —C— or —S—	
R ¹ = alquilo inferior	NO	

		párrafo 6)
$R^2 = \text{H, halo, nitro, ciano}$	H (pág. 1 párrafos 5 y 6)	H, halo, nitro, ciano (pag. 1 párrafo 6)
$R^3 = \text{Cicloalquilo de 4 a 6 miembros}$	Cicloalquilo de 5 a 7 miembros H. (pág. 1 párrafos 5 y 6)	Cicloalquilo de 5 a 7 miembros (pag. 1 párrafo 6)

4) Estado de la Técnica más cercano es D1

La solicitud se diferencia de D1 en que presenta ligeras variaciones en el significado de los sustituyentes R^1 y R^4 de la presente solicitud.

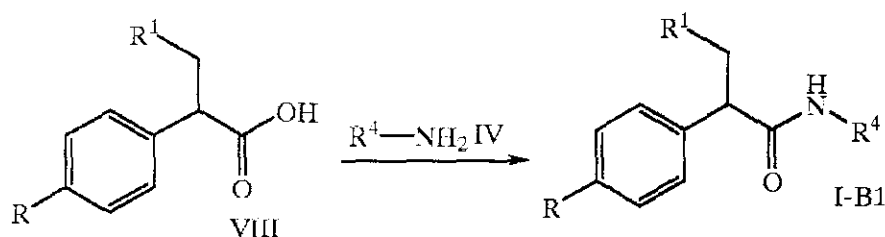
El Efecto Técnico que logra la diferencia es inferior al de las anterioridades, ya que tanto D1 como D2 reportan en el ensayo de actividad de la glucoquinasa in vitro que el $SC_{1.5}$ de los compuestos ensayados es menor o igual a $30\mu\text{M}$ (D1 página 34 párrafo 0268; D2 página 30 párrafo 0173), mientras que los compuestos de la presente solicitud poseen valores de $SC_{1.5}$ de hasta de $100\mu\text{M}$.

El Problema Técnico Objetivo de esta solicitud consiste en realizar modificaciones a la estructura que presentan D1 y D2 y obtener compuestos alternativos útiles como activadores de la glucoquinasa.

En conclusión es evidente para el experto en la materia realizar ligeras modificaciones a la estructura que enseña D1 y D2 para lograr compuestos que conserven la misma actividad. Por lo tanto las reivindicaciones 1 a 67, 72 y 74 carecen de nivel inventivo.

De la misma forma las composiciones de las reivindicaciones 68 a 71 no son inventivas puesto que los compuestos que las caracterizan no son inventivos.

Igualmente, D1 divulga diversas reacciones para la obtención de los compuestos que enseña (pág. 4 párrafo 0051), entre las cuales se tiene la reacción de un derivado del ácido fenil acético con una amina sustituida:



Por lo tanto el procedimiento para la preparación de los compuestos reclamados en la reivindicación 73 no es inventivo ya que se fundamenta en un proceso de síntesis conocido para la obtención de fenil acetamidas heteroaril sustituidas.

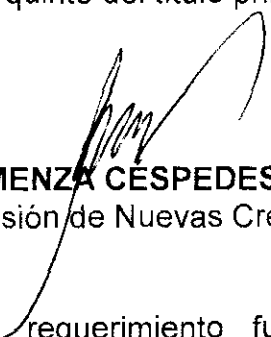
6. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

N°	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US2002/0002190	1-74	Nivel Inventivo
D2	US2002/0042512	1-74	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.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

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

23 ENE 2002

CONCEPTO TÉCNICO No. 3179	EXAMINADOR TÉCNICO Código No. 202073
-------------------------------------	--